THERAPEUTIC ADVANCES in
Hematology

Original Research

A phase I/II study of gilteritinib in combination with chemotherapy in newly diagnosed patients with AML in Asia: final analysis

Ther Adv Hematol

2026, Vol. 17: 1–13

DOI: 10.1177/20406207261419953

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Abstract

Background: Mutations in the *FMS*-like tyrosine kinase 3 (*FLT3*) gene are present in approximately 30% of patients with newly diagnosed (ND) acute myeloid leukemia (AML), and are associated with worse therapy outcomes compared to the general AML population. Gilteritinib, a selective oral FLT3 inhibitor, is a promising treatment option for this patient population.

Objectives: To assess the safety and efficacy of gilteritinib in combination with induction and consolidation chemotherapy in Asian patients with ND, *FLT3*-mutated (*FLT3*^{mut}+) AML.

Design: This study was a phase I/II open-label, single-arm study. Herein, we present the final results from phase II.

Methods: A total of 84 patients were enrolled in 33 centers across Japan, Korea, and Taiwan. All patients enrolled in phase II received induction and consolidation therapy with gilteritinib 120 mg/day plus chemotherapy (induction: ⩽2 cycles, idarubicin/cytarabine once-daily; consolidation: ⩽4 cycles, cytarabine twice-daily) followed by maintenance with gilteritinib 120 mg/day monotherapy (⩽26 cycles). The primary efficacy endpoint was the complete remission (CR) rate after induction therapy.

Results: The primary endpoint of CR rate after induction was 50.0% (90% CI: 40.4–59.6). Gilteritinib in combination with chemotherapy achieved high composite CR (CRc; 86.6%, 95% CI: 77.3–93.1) rates after induction. The overall survival (OS) rate at 3 years was 71.6%, and the median OS was 48.2 months; however, due to the immaturity of the data, the median OS should be interpreted with caution. In addition, 51.2% of patients underwent hematopoietic stem cell transplantation during the study period. The safety profile of gilteritinib was as expected, and no new safety signals were identified.

Conclusion: Induction and consolidation with gilteritinib plus chemotherapy, and maintenance with gilteritinib monotherapy were well tolerated in ND patients in Asia with *FLT3*^{mut}+ AML and had favorable efficacy compared with historical data.

Trial registration: This trial was registered with the ClinicalTrials.gov identifier NCT02310321.

Keywords: acute myeloid leukemia, Asia, combination therapy, *FLT3* mutations, gilteritinib, maintenance, transplant-eligible

Received: 4 September 2025; revised manuscript accepted: 8 January 2026.

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Introduction

Acute myeloid leukemia (AML) is the most common subtype of myeloid leukemia in adults worldwide,[1] with East Asia constituting one of the top three regions with the highest incidence, along with high-income North America and Western Europe.[2] AML is associated with high rates of morbidity and mortality, with a more pronounced disease burden in the elderly and male populations.[3] Mutations in the *FMS*-like tyrosine kinase 3 (*FLT3*) gene, either internal tandem duplication (*FLT3*-ITD) or tyrosine kinase domain (*FLT3*-TKD) mutations, are observed in approximately 30% of patients with newly diagnosed (ND) AML, and are associated with particularly poor prognoses.[4] Furthermore, patients with *FLT3*-ITD mutations experience worse therapy outcomes compared to the general AML population, with higher rates of relapse and a shorter overall survival (OS).[4] Therefore, there is an unmet need for alternative therapies in patients with ND AML who carry *FLT3*-ITD and/or *FLT3*-TKD mutations (*FLT3*-ITD/TKD^{mut}+ AML).

Gilteritinib is a selective oral FLT3 inhibitor for the treatment of AML with activity against *FLT3*-ITD and *FLT3*-TKD mutations.[5] The safety and efficacy of gilteritinib monotherapy versus salvage chemotherapy in patients with relapsed or refractory (R/R) *FLT3*^{mut}+ AML have been previously reported in the phase III ADMIRAL and COMMODORE studies.[5,6] As a result, gilteritinib was approved by the European Medicines Agency,[7] the US Food and Drug Administration,[8] and the Ministry of Health Labor and Wealth in Japan[9] for the treatment of patients with R/R *FLT3*^{mut}+ AML.

A phase I/II open-label, single-arm study of gilteritinib in combination with induction and consolidation chemotherapy was conducted in Asian patients with ND AML.[10] Interim analysis results from phase I and II reported that gilteritinib in combination with chemotherapy was well tolerated, with similar composite complete remission (CRc) rates to previous studies.[10] Herein, we present the final results from phase II of this study, with 40.5 months of OS follow-up, which assessed the safety and efficacy of gilteritinib in combination with chemotherapy in patients with ND, *FLT3*$^{mut+}$ (*FLT3*-ITD/TKD^{mut}+) AML.

Methods

Study design

Details on study design have been previously reported.[10] In the phase II portion of this phase I/II, open-label, single-arm study (NCT02310321), 84 patients in the safety analysis set (SAF) were enrolled in 33 out of 52 centers across Japan, Korea, and Taiwan. All patients enrolled in phase II received gilteritinib at the recommended dose established in the phase I part of the study. Patients received gilteritinib 120 mg/day, with 7+3 induction (⩽2 cycles, idarubicin/cytarabine once-daily) and consolidation (⩽4 cycles, cytarabine twice-daily) chemotherapy, followed by maintenance (⩽26 cycles) gilteritinib 120 mg/day monotherapy. Patients who were eligible for hematopoietic stem cell transplantation (HSCT) were permitted to undergo HSCT after or without consolidation therapy, and continued to receive maintenance therapy without leaving the study if specified criteria were met. The follow-up period was 3 years from treatment initiation for the last enrolled patient or completion of 30-day follow-up of the last patient(s), whichever was longer.

Patients

Eligibility criteria have been previously published.[10] Specifically for phase II, eligible patients were adults as per local regulations at the time of consent and were ND with AML according to the World Health Organization classification (2017) within 28 days prior to enrollment. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ⩽2; patients with an ECOG PS of 2 were eligible for the phase II study part only if investigators believed that their PS score was primarily due to symptoms of their underlying disease. Patients were required to meet protocol-specified clinical laboratory test criteria.[10] In addition, patients were positive for *FLT3*-ITD or *FLT3*-TKD mutations, determined by PCR-based assay from bone marrow or whole blood samples, and had aspartate aminotransferase or alanine aminotransferase $<3\times$ upper limit of normal and serum magnesium ⩾institutional lower limit of normal.

Patients with a diagnosis of acute promyelocytic leukemia or *BCR-ABL1*-positive leukemia

(chronic myeloid leukemia in blast crisis), or active malignant tumors other than AML or myelodysplastic syndrome, or clinically active central nervous system leukemia were excluded.

Endpoints

Study endpoints have been previously described.[10] In the phase II part of this study, the primary efficacy endpoint was the complete remission (CR) rate after induction therapy. Specific secondary efficacy endpoints for phase II included: OS, defined as the time from the start date to the date of death due to any cause; event-free survival (EFS), defined as the time from start date of the treatment until the date of documented relapse, treatment failure or death; relapse-free survival (RFS), defined as the time from the date of first CRc until the date of documented relapse or death for participants who achieved CRc; CR rate after each treatment therapy, defined as a morphologically leukemia-free state with full hematologic recovery (defined as neutrophil count $\geq$1000/mm^3, platelet count $\geq$100,000/mm^3, bone marrow blasts $<$5%; no evidence of Auer rods and extramedullary leukemia, and peripheral blood blast count $\leq$2%); CR rate without minimal residual disease (MRD) after each treatment therapy, MRD negativity was defined as a summed *FLT3*-ITD signal ratio $\leq 10^{-4}$ for $\geq$1 postbaseline sample.

MRD was determined using a PCR-amplified next-generation sequencing method that provides the sensitivity to detect $\geq$1 *FLT3*-ITD–containing leukemic cell among 10,000 cells containing the wild-type allele;[11] CR with partial hematologic recovery (CRh) rate after each treatment therapy, defined as a condition with bone marrow blasts $<$5%, neutrophil count $\geq$500/mm^3, platelet count $\geq$50,000/mm^3, no evidence of extramedullary leukemia, and peripheral blood blast count $\leq$2%, and that also could not be classified as CR; CRc rate after each treatment therapy, defined as achievement of one of CR, CR with incomplete platelet recovery (CRp) or CR with incomplete hematologic recovery (CRi), where CRp was defined as a condition that met all of the CR criteria at the postbaseline visit, except for the unrecovered platelet count ($<$100,000/mm^3) and CRi was defined as a condition that met all CR criteria at the postbaseline visit, except for an unrecovered neutrophil count ($<$1000/mm^3), and regardless of whether platelet count was recovered; CR/CRh, defined as achievement of conditions for either CR or CRh, respectively.

In addition, pharmacokinetic (PK) parameters of gilteritinib concomitant with induction and consolidation chemotherapy were characterized. Phase II secondary safety endpoints included adverse events (AEs), which were coded using the Medical Dictionary for Regulatory Activities (MedDRA v23.0) and graded using the National Cancer Institute (Common Terminology Criteria v4.0 for Adverse Events (NCI-CTCAE)).[12] Exploratory endpoints included time to hematologic recovery after a treatment cycle, defined as the time from the start date of the treatment for each treatment cycle until the date of neutrophil count $\geq$1000/mm^3 and platelet count $\geq$100,000/mm^3. Patients with none of these events were censored at the date of last assessment. Additional exploratory endpoints included transplantation rate, overall MRD negativity by treatment period, and MRD-negative CR rate for any treatment period.

Statistical analyses

Statistical analyses of efficacy, safety, and PK were previously described.[10] Primary efficacy analyses were conducted in the full analysis set (FAS), comprising all patients who received $\geq$1 dose of the study drug and had $\geq$1 postbaseline bone marrow assessment. In phase II, the target sample size was 80 patients. An evaluable sample size of 70 patients was expected to yield $>$80% power to detect a 15% increase in CR rate from 55%, benchmark based on the placebo arm of the RATIFY study,[13] to 70% at a 1-sided significance level of 0.05. Assuming an approximately 10% drop-out rate, a total of 80 subjects would be enrolled in the Phase II part. The 2-sided 90% exact confidence interval (CI) was calculated by the Clopper-Pearson method. Out of 70 evaluable participants, at least 46 participants who achieved CR after induction were necessary to exclude 55% based on the 90% exact CI of CR. For secondary efficacy endpoints, survival rates (OS, EFS, and RFS) were described using the Kaplan-Meier method for time-to-event (TTE) outcomes. TTE endpoints were analyzed in the TTE-FAS, which comprised all participants who received $\geq$1 dose of gilteritinib, independently of postbaseline bone marrow assessment. Binary endpoints for rates of remission (rates of CR,

CRc, CRp, CRi, and CR/CRh) were described using a 2-sided 95% exact CI. Median duration of OS follow-up with 2-sided 95% CI was calculated using the reverse Kaplan-Meier method. MRD analyses were conducted in the MRD analysis set (MAS), comprising all registered patients who received ⩾1 dose of gilteritinib, were confirmed as *FLT3*-ITD–positive at screening, and had a baseline and ⩾1 postbaseline sample with MRD data. Of note, CR rates without MRD were analyzed in the FAS, which included patients without a postbaseline MRD sample, who were considered nonresponders. Safety analyses were conducted in the SAF, comprising all patients who received ⩾1 dose of gilteritinib. PK analyses were conducted in all patients who received ⩾1 dose of the study drug, and had available drug concentration data for ⩾1 time point after drug initiation. All statistical analyses were conducted using the SAS (Version 9.4 or higher) software package (Cary, NC, USA).

Results

Patient disposition, demographics, and baseline characteristics

In phase II, out of 212 patients who were preregistered and received chemotherapy, 84 were registered, received gilteritinib, and were included in the SAF. The number of patients included in each analysis population is provided in Supplemental Table S1. Of the 84 patients who received gilteritinib in the phase II part of the study, 62 (73.8%) completed the induction period and 22 (26.2%) discontinued the induction treatment (Supplemental Figure S1); of those, six discontinued due to physician decision, four due to patient withdrawal, three due to death, three due to lack of efficacy, two due to AEs, two due to disease relapse, and two due to reasons classified as "Other." Of the 62 patients who completed the induction period, 57 (91.9%) entered the consolidation period; of those, 42 (73.7%) proceeded on to maintenance therapy and 15 (26.3%) discontinued study treatment (four due to physician decision, four due to disease relapse, and seven due to reasons classified as "Other"). A total of 46 patients entered the maintenance period, including four patients who underwent HSCT without entering the consolidation period, and entered the maintenance period after HSCT. Of these 46 patients, 23 (50.0%) discontinued study treatment (11 due to disease relapse, 6 due to physician decision, 3 due to AEs, 1 due to death, and 2 due to reasons classified as "Other") and 23 (50.0%) completed the maintenance period (up to 26 cycles; 28 days/cycle).

Baseline demographics and disease characteristics were previously reported.[10] Out of 84 patients, 48.8% were male; all were Asian; median (range) age was 52.0 (20–77) years, and 81.0% were ⩽65 years of age. More than half of the patients (57.1%) had an ECOG PS of 1. All patients in phase II carried *FLT3* mutations, and positive status for *FLT3*-ITD and *FLT3*-TKD mutations was observed in 69 (82.1%) and 20 (23.8%) patients, respectively.

Efficacy

The primary endpoint of the CR rate after induction was previously reported.[10] In patients with ⩾1 postbaseline assessment ($n = 82$), the CR (90% CI) rate after induction was 50.0% (40.4–59.6); therefore, the lower limit of a 2-sided 90% CI did not reach the predefined benchmark rate of 55% (Table 1). However, the best overall response for CR (95% CI) increased to 63.4% (52.0–73.8) after consolidation, and remained unchanged after maintenance. The CRc (86.6%, 95% CI: 77.3–93.1) and CR/CRh (67.1%, 95% CI: 55.8–77.1) rates were high after induction, and CRc rates remained stable after consolidation (87.8%, 95% CI: 78.7–94.0) and maintenance (87.8%, 95% CI: 78.7–94.0). The transition of CR and CRc rate was due to an increasing number of patients transitioning from CRp/CRi to CR from induction to consolidation therapy. The CR (95% CI) rate without MRD was 18.3% (10.6–28.4) after induction and 35.4% (25.1–46.7) after consolidation, and was unchanged after maintenance. The CRc rate without MRD negativity (95% CI) in the FAS was 23.2% (14.6–33.8) after induction, increasing to 41.5% (30.7–52.9) after both consolidation and maintenance. These results were consistent with the reported response rates in the interim analysis.[10] Based on subgroup analyses, the CR rate (90% CI) after induction was higher in patients with *FLT3*-ITD mutation (50.7% (40.1–61.4)) than in patients with *FLT3*-TKD mutation (40.0% (21.7–60.6)).

Survival

The probability of OS (95% CI) rate at 3 years in the TTE-FAS was 71.6% (60.1–80.3), and the

Table 1. Derived response assessments after induction, consolidation, and maintenance therapy.

BOR, *n* (%) (95% CI)[a]	Phase II patients (*N* = 82)		
	After induction therapy	After consolidation therapy	After maintenance therapy
CR	41 (50.0) (38.7–61.3)	52 (63.4) (52.0–73.8)	52 (63.4) (52.0–73.8)
CRp	11 (13.4) (6.9–22.7)	8 (9.8) (4.3–18.3)	8 (9.8) (4.3–18.3)
CRi	19 (23.2) (14.6–33.8)	12 (14.6) (7.8–24.2)	12 (14.6) (7.8–24.2)
CRc rate	71 (86.6) (77.3–93.1)	72 (87.8) (78.7–94.0)	72 (87.8) (78.7–94.0)
Response rate	75 (91.5) (83.2–96.5)	76 (92.7) (84.8–97.3)	76 (92.7) (84.8–97.3)
CR/CRh rate	55 (67.1) (55.8–77.1)	60 (73.2) (62.2–82.4)	60 (73.2) (62.2–82.4)
CR rate without MRD negativity	15 (18.3) (10.6–28.4)	29 (35.4) (25.1–46.7)	29 (35.4) (25.1–46.7)
CRc rate without MRD negativity	19 (23.2) (14.6–33.8)	34 (41.5) (30.7–52.9)	34 (41.5) (30.7–52.9)

For participants who underwent HSCT, only response assessment data before HSCT were included in this table.
[a]95% exact CI was estimated using the binomial distribution.
BOR, best overall response; CI, confidence interval; CR, complete remission; CRc, composite complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; CRp, complete remission with incomplete platelet recovery; HSCT, hematopoietic stem cell transplantation; MRD, minimal residual disease.

median OS (95% CI) was 48.2 months (45.1–not evaluable (NE)), with only two participants remaining at risk at 48 months (Figure 1(a)). Due to the immaturity of the data, the median OS should be interpreted with caution. In subgroup analysis, the OS (95% CI) rate at 3 years in patients with *FLT3*-ITD and *FLT3*-TKD mutations was 75.3% (62.9–84.1) and 58.5% (31.7–77.9), respectively (Supplemental Table S2). EFS events in the TTE-FAS occurred in 39 (46.4%) patients, and the median EFS (95% CI) was 25.0 months (11.3–48.2; Figure 1(b)). The median RFS (95% CI) in the FAS was 27.8 months (17.4–39.8; Supplemental Table S3).

MRD, HSCT rate, and hematologic recovery

MRD negativity in the MAS was achieved in 35 (55.6%) patients (Supplemental Table S4). The MRD negativity rate was numerically higher after the consolidation ($n = 28/36$ (77.8%)) than after the induction ($n = 22/58$ (37.9%)) period. The majority of MRD-negative patients (>70%) achieved CR by the end of the consolidation period, while fewer than half of MRD-positive participants achieved CR by the end of the maintenance period.

Overall, 51.2% ($n = 42/82$) of patients in the FAS underwent HSCT during the study period, and the median (95% CI) time to hematopoietic recovery after Cycle 1 of the induction period was 48.0 days (46.0–57.0; Table 2). Based on subgroup analyses, the HSCT rate was higher in patients with *FLT3*-ITD mutations ($n = 40/67$ (59.7%)) than in patients with *FLT3*-TKD ($n = 4/20$ (20.0%)) and *FLT3*-ITD/TKD mutations ($n = 2/5$ (40.0%); Supplemental Table S5). The HSCT rate was 61.2% among patients <65 years of age. When censoring at HSCT, the OS rate at 3 years was 66.4% and the median OS was NE (Supplemental Figure S2).

Safety

The overall safety profile was consistent with the interim analysis (Table 3).[10] The most commonly reported treatment-emergent adverse events (TEAEs) in the SAF were febrile neutropenia (57/84 patients (67.9%)), pyrexia (43/84 patients (51.2%)), and increased alanine aminotransferase (37/84 patients (44.0%); Table 4). Out of 84 patients, 80 (95.2%) patients experienced grade ⩾3 TEAEs; the most frequent were febrile neutropenia (57/84 patients (67.9%)) and decreased platelet count (29/84 patients (34.5%)). Serious TEAEs were reported in 45/84 patients (53.6%); the most commonly reported serious TEAEs were sepsis and pneumonia (9/84 patients (10.7%) each); febrile neutropenia (5/84 patients (6.0%)); and abnormal hepatic function (6/84 patients (7.1%)). TEAEs leading to withdrawal of treatment were reported in 7/84 patients (8.3%), and included abnormal hepatic function, acute graft versus host disease in the liver, pneumonia, septic shock, increased gamma-glutamyltransferase, decreased platelet count, and gastric cancer (1/84 patients (1.2%) each). The number of deaths due to TEAEs remained the same as in the interim analysis (4/84 patients (4.8%)).[10]

Pharmacokinetics

The mean (standard deviation (SD)) trough concentration of gilteritinib in the induction period was 522 (331) ng/mL on Cycle 1 Day 15 and 647 (518) ng/mL on Cycle 1 Day 21. The mean (SD) trough concentration in the consolidation period was 244 (152) ng/mL on Cycle 1 Day 8 and 375 (249) ng/mL on Cycle 1 Day 15.

Discussion

In this final analysis of the phase II portion of a phase I/II study, gilteritinib plus chemotherapy was well tolerated in ND patients in Asia with *FLT3*$^{mut+}$ AML. While this study did not meet its primary endpoint of CR rate at the end of induction, other efficacy endpoints, including CRc rate, transplantation rate, and OS, compare favorably with published data.[13,14]

It should be noted that the prespecified benchmark for meeting the primary endpoint was based on the placebo arm of the RATIFY study;[13] thus, some notable differences in study design may have impacted the primary endpoint of CR, thereby limiting direct efficacy comparisons. In the RATIFY study, bone marrow examination was performed on Day 21 of the induction period to assess the need for a second induction cycle; if bone marrow assessment revealed <5% of leukemic blasts in the cellular marrow (>20%), a second assessment was performed within 1 week after recovery of ANC ⩾1000/μL and platelets ⩾100,000/μL to assess for response and to document CR. This exam had to have been performed no later than Day 60 after starting protocol treatment.[13] In addition, patients with residual AML after second remission induction were removed from protocol therapy, while those who achieved complete response proceeded to consolidation therapy.

In contrast, in the present study, efficacy assessments were performed any time on or after Day 28 in Cycle 1 of induction therapy, prior to initiation of consolidation therapy, and thereafter during maintenance according to institutional guidelines. No bone marrow assessments after hematologic recovery (ANC ⩾1000/μL and platelets ⩾100,000/μL) at the end of induction were mandated by the protocol—this is in contrast to the RATIFY design described above, which aimed to ensure documentation of all CR events.[13] In addition, no hematologic recovery threshold was set for progression to consolidation therapy in this study; thus, patients with only CRp/CRi could proceed to consolidation therapy, which may have reduced the CR rate postinduction compared to the RATIFY study. Consequently, it is necessary to consider these differences in protocol settings and regional medical practices when comparing study outcomes. Of note, the CR rate in this study was similar to those reported in the global phase III QuANTUM-First study of patients with *FLT3*-ITD AML receiving either quizartinib plus chemotherapy (54.9%) or placebo plus chemotherapy (55.4%).[14]

Gilteritinib in combination with chemotherapy achieved high CRc (86.6%, 95% CI: 77.3–93.1) and CR/CRh (67.1%, 95% CI: 55.8–77.1) rates after induction, suggesting that most patients had achieved partial hematologic recovery. In addition, the CR rate increased from 50.0% after induction to 63.4% after consolidation and after maintenance, due to an increasing number of patients transitioning from CRp/CRi to CR from induction to consolidation therapy; these were maintained from the previously reported interim

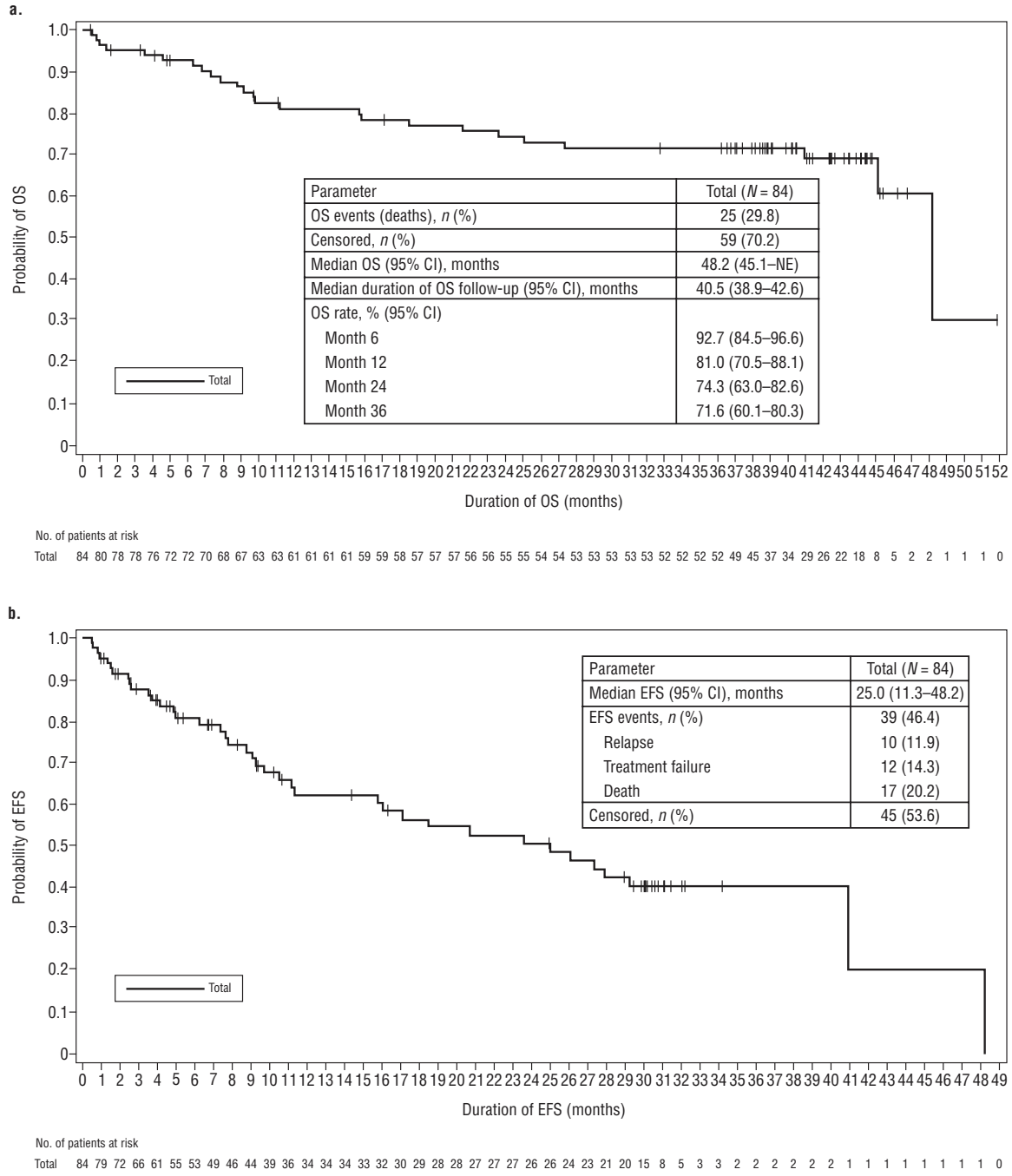

Figure 1. Kaplan-Meier plot of OS (a) and EFS (b).
CI, confidence interval; EFS, event-free survival; NE, not evaluable; OS, overall survival.

analysis.[10] These results were similar to those in a preceding phase Ib study in the United States, which reported a CRc rate after 1 induction cycle of 89% for patients with *FLT3*^{mut}+ AML.[15] In addition, in an ad hoc analysis conducted to align the definition of CRi with the QuANTUM-First study (i.e., requirement for platelet recovery ($\geq$100,000/mm^3) and response within 60 days following Day 1 of the last day of induction cycle), the obtained CRc rate after induction (69.5%) was comparable to the CRc rates of the quizartinib plus chemotherapy (71.6%) and placebo plus chemotherapy (64.9%) arms in the QuANTUM-First study.[10,14]

Table 2. Transplantation rate and time to hematopoietic recovery during the induction period Cycle 1.

Parameter	Total (*N* = 82)
Transplantation, *n* (%)	
No	40 (48.8)
Yes	42 (51.2)
Median time to hematopoietic recovery (95% CI), days[a]	48.0 (46.0–57.0)
Range	14+, 89+

Time to hematopoietic recovery after each treatment cycle was defined as the time from the start date of the treatment for each treatment cycle until the date of having a neutrophil count of ⩾1000/mm^3 and platelet count of ⩾100,000/mm^3. Participants with none of these events were censored at the date of last assessment.
[a]Based on Kaplan-Meier estimates.
"+" indicates censoring.
CI, confidence interval.

Table 3. Overview of TEAEs and deaths.

Parameter	Total (*N* = 84), *n* (%)
Any TEAEs	84 (100)
Grade 3 or higher TEAEs	80 (95.2)
Serious TEAEs[a]	45 (53.6)
TEAEs leading to withdrawal of treatment	7 (8.3)
TEAEs leading to death	4 (4.8)
Death[b]	25 (29.8)

[a]Includes serious adverse events upgraded by the sponsor based on review of the Sponsor's list of Always Serious terms, if any upgrade was done.
[b]All reported deaths after the first gilteritinib administration.
TEAE, treatment-emergent adverse event.

The OS rate at 3 years was 71.6%, and the median OS was 48.2 months. When compared to the median OS in the placebo plus chemotherapy arms of the RATIFY and QuANTUM-First studies (25.6 and 15.1 months, respectively),[13,14] the combination of gilteritinib with chemotherapy may contribute to extend OS compared to chemotherapy alone. However, there are several limitations in comparing TTE analysis results among multiple studies. In addition, due to the small number of patients contributing to the result, with only two patients at risk at 48 months, the median OS is considered immature and should be interpreted with caution.

In addition, MRD negativity was achieved in over half of the (n = 35/63 (55.6%)), likely contributing to the favorable survival outcomes. Moreover, the transplantation rate was 51.2% (61.2% among patients <65 years of age), which was numerically higher than those observed in both the quizartinib (38.1%) and placebo (33.6%) arms after induction and consolidation therapy of the QuANTUM-First study, and comparable to the midostaurin (59.2%) and placebo (55.0%) arms after induction, consolidation, and maintenance therapy of the RATIFY study.[13,14] Transplantation is generally considered a curative treatment option for patients with AML who are physically able to tolerate the procedure, associated with better overall survival and a reduced risk of relapse.[16] Higher transplantation rates in a clinical trial are therefore considered beneficial for the patient population. Differences in protocol specifications and patient demographics (e.g., median age) may limit comparisons of HSCT rates between studies.

It should be noted that the 3-year OS rate was numerically higher without censoring at HSCT compared to the rate with censoring at HSCT (71.6% vs 66.4%), supporting the beneficial effect of HSCT on survival. In subgroup analyses, the overall transplantation rate was higher for patients with *FLT3*-ITD mutations (59.7%) than for patients with *FLT3*-TKD mutations (20.0%). This difference may be attributed to the poorer prognosis of *FLT3*-ITD mutations compared to *FLT3*-TKD mutations; however, the prognostic impact of *FLT3*-TKD mutations remains controversial.[17,18] Due to the small sample size in each subgroup, these findings should be interpreted with caution. The median time to hematopoietic recovery was 48.0 days (95% CI: 46.0–57.0) after Cycle 1 of the induction period. A previous phase III study reported a faster hematopoietic recovery (31–35, calculated based on published data) in patients with ND AML after receiving chemotherapy alone.[19] In contrast, other studies of FLT3 inhibitors reported similar delays in hematopoietic recovery, including a phase Ib study of gilteritinib combined with 7 + 3 cytarabine/idarubicin

Table 4. Most common TEAEs occurring in ⩾15% of patients.

Adverse event	Total (*N* = 84), *n* (%)	
	Any grade	Grade ⩾3
Febrile neutropenia	57 (67.9)	57 (67.9)
Pyrexia	43 (51.2)	5 (6.0)
Alanine aminotransferase increased	37 (44.0)	17 (20.2)
Constipation	35 (41.7)	1 (1.2)
Diarrhea	33 (39.3)	2 (2.4)
Rash	32 (38.1)	1 (1.2)
Hypokalemia	29 (34.5)	13 (15.5)
Platelet count decreased	29 (34.5)	29 (34.5)
Aspartate aminotransferase increased	28 (33.3)	11 (13.1)
Nausea	27 (32.1)	1 (1.2)
Neutrophil count decreased	27 (32.1)	27 (32.1)
Stomatitis	25 (29.8)	1 (1.2)
Anemia	22 (26.2)	20 (23.8)
Pneumonia	22 (26.2)	12 (14.3)
Headache	18 (21.4)	0
Bacteremia	17 (20.2)	8 (9.5)
Vomiting	16 (19.0)	0
Insomnia	16 (19.0)	0
Alopecia	15 (17.9)	0
White blood cell count decreased	15 (17.9)	15 (17.9)
Hepatic function abnormal	14 (16.7)	5 (6.0)
Allergic transfusion reaction	13 (15.5)	2 (2.4)
Thrombocytopenia	13 (15.5)	13 (15.5)

TEAE, treatment-emergent adverse event.

versus cytarabine/daunorubicin induction remission (median 41 days), and the QuANTUM-First study of quizartinib combined with chemotherapy versus chemotherapy alone (median 36 days).[14,15] These findings suggest an effect of FLT3 inhibitors on hematologic recovery. However, differences in the methodologies used for assessing hematologic recovery limit comparisons between studies.

The safety profile of gilteritinib was as expected for patients with newly diagnosed AML, and no new safety signals were identified compared to other FLT3 inhibitors.[13,14] The rate of serious AEs (53.6%) was similar to that in the quizartinib arm of the QuANTUM-First study (54%), and similar rates of grade ⩾3 AEs were reported across studies.[13,14] Therefore, gilteritinib in combination with cytarabine/idarubicin as induction

therapy and gilteritinib plus high-dose cytarabine as consolidation therapy was well tolerated in this patient population.

The results of this study further establish gilteritinib monotherapy as a preferred post-HSCT maintenance treatment for MRD-positive *FLT3*^{mut}+ AML per the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®),[20] providing additional support to previous reports from the MORPHO trial, in which gilteritinib monotherapy was associated with a higher relapse-free survival rate in patients with *FLT3*-ITD mutations and MRD detectable pre or post HSCT.[21]

An important strength of the present study is the enrollment of patients with either *FLT3*-ITD or *FLT3*-TKD mutations. Similarly, this study allowed the inclusion of patients >60 years of age, and the continued inclusion of patients post HSCT, which were excluded from the RATIFY study. In addition, the median OS follow-up of this study was 40.5 months, which allowed for a longer assessment of survival outcomes, such as mature OS rate at 3 years (71.6%), although the median OS (48.2 months with only two patients at risk at 48 months) was still immature. Finally, next-generation sequencing to determine MRD after gilteritinib treatment was used in order to provide enhanced sensitivity for the detection of *FLT3* mutations.[11]

Limitations

Some key limitations in this study were the differences in protocol setting and regional practices between Asia and the United States/European Union. For instance, patients could transition to HSCT prior to reaching full hematologic recovery; these events happened frequently, in turn artificially decreasing the CR rate by the end of induction. In addition, this study did not include a comparator arm; thus, the CR rate was evaluated based on the placebo arm of the RATIFY study.[13] The lack of a randomized controlled arm and subsequent reliance on a historical benchmark allows only indirect efficacy comparisons.

Future directions

Additional ongoing trials are investigating gilteritinib in patients with ND *FLT3*^{mut}+ AML. The HOVON 156 AML trial compares gilteritinib versus midostaurin combined with induction and consolidation chemotherapy in patients eligible for intensive chemotherapy.[22] Another ongoing single-center phase I/II trial is evaluating azacitidine, venetoclax, and gilteritinib in patients with ND *FLT3*^{mut}+ AML unfit for intensive chemotherapy; preliminary findings show a high rate of CR/CRi (96%) and 65% of patients achieving MRD negativity within four cycles.[23] Finally, the ongoing, multi-center phase I/II VICEROY trial is evaluating gilteritinib, venetoclax, and azacitidine in ND *FLT3*^{mut}+ AML unfit for intensive chemotherapy.[24]

Conclusion

Altogether, these findings suggest that gilteritinib in combination with cytarabine/idarubicin as induction chemotherapy, high-dose cytarabine as consolidation chemotherapy, and gilteritinib monotherapy as maintenance therapy were well tolerated in participants with newly diagnosed AML and had favorable efficacy compared with historical data.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with Good Clinical Practice and consensus ethical principles derived from international guidelines, including the Declaration of Helsinki, Council for International Organizations of Medical Sciences international ethical guidelines, and applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guidelines for Good Clinical Practice and was approved by the Kobe City Medical Center General Hospital Certified Review Board (Institutional Review Board number: 治17-04) on October 1, 2019. The protocol and any amendments were reviewed and approved by an Institutional Review Board or Independent Ethics Committee at each study site prior to study commencement. Written informed consent was provided by each patient prior to initiation of any study-related procedures.

Consent for publication

The authors confirm that written informed consent for publication of the clinical details as described in this manuscript was obtained from the patients.

Author contributions

Masashi Sawa: Data curation; Writing – original draft; Writing – review & editing.

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Hee-Je Kim: Data curation; Writing – original draft; Writing – review & editing.

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Acknowledgments

This study was initiated and funded by Astellas Pharma Inc. Medical writing support was provided by Patricia Rosell Arevalo, PhD of Lumanity Scientific Inc., funded by Astellas Pharma Inc. in accordance with Good Publication Practice (GPP 2022) guidelines (http://www.ismpp.org/gpp-2022).

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was initiated and funded by Astellas Pharma Inc. Medical writing support was funded by Astellas Pharma Inc.

Competing interests

Sawa M reports payment/honoraria from Janssen Pharma and Sanofi. Miyamoto T reports payment/honoraria from Takeda Pharmaceutical Co., Otsuka Pharmaceutical Co., Ltd., MSD Co., Ltd, Astellas Pharmaceutical Co., Ltd., Janssen Co., Ltd., AbbVie Pharmaceutical Co., Ltd., and Kyowa Kirin Pharmaceutical Co. Kim H-J reports consulting fees from AbbVie, Astellas, AML Hub, Bristol Myers Squibb&Celgene, Daiichi Sankyo, Janssen, Handok, Jazz, Novartis, Pfizer, Takeda, Sanofi-Genzyme, Meiji, GreenCross, MSD; honoraria from AbbVie, Astellas, Bristol Myers Squibb&Celgene, Jazz, Sanofi-Genzyme, Novartis, Takeda; participated in advisory boards for AbbVie, Astellas, AML Hub, Novartis, Sanofi-Genzyme, MSD, Takeda, and acted in a leadership/trustee role for AML Hub, Asia Pacific Blood and Marrow Transplant Group, Asia Pacific Leukemia Consortium, and The Korean Society of Blood and Marrow Transplantation. Cheong J-W reports payment/honoraria from Astellas, Bristol Myers Squibb, Merck, and GSK, and acted in a leadership/trustee role for The Korean Society of Hematology, AML/MDS Working Party, and The Korean Society of Blood and Marrow Transplantation. Naoe T reports payment/honoraria from Bristol Myers Squibb, Pfizer, Nippon Shinyaku, Astellas, Otsuka Pharmaceutical Co., Ltd., and Japan Tissue Engineering. Akashi K reports grants from Asahi Kasei Pharma, Chugai Pharmaceutical, Kyowa Kirin Pharmaceutical Co., and Sumitomo

Pharma, and payment and/or honoraria from Asahi Kasei Pharma, Astellas, AstraZeneca, AbbVie, Kyowa Kirin Pharmaceutical Co., Chugai Pharmaceutical, Bristol Myers Squibb, and Janssen Pharmaceuticals. Kosako M was an employee of Astellas Pharma Inc. until the research was conducted. Shimura M, Terada W, Kadokura T, Gill SC, Heinloth A, Hill J, and Hasabou N are employees of Astellas Pharma Inc. Ikezoe T is editor of *International Journal of Hematology*. Hiramatsu Y, Morita S, and Miyawaki S have no disclosures to report.

Availability of data and materials

Researchers may request access to anonymized patient-level data, trial-level data, and protocols from Astellas-sponsored clinical trials at https://www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing, see: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx.

Supplemental material

Supplemental material for this article is available online.

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