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Clinical profile of gilteritinib in Japanese patients with relapsed/refractory acute myeloid leukemia: An open-label phase 1 study

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Gilteritinib, a novel, highly specific, potent *fms*-like tyrosine kinase 3/AXL inhibitor, demonstrated antileukemic activity in patients with relapsed/refractory (R/R) acute myeloid leukemia (AML). In this open-label phase 1 study (NCT02181660), Japanese patients (aged ≥18 years) with R/R AML received once-daily gilteritinib, escalating from 20 to 300 mg/d. Primary endpoints were safety/tolerability, including the maximum tolerated dose (MTD) and the recommended dose (RD); secondary endpoints were antileukemic activity and pharmacokinetics (PK). Twenty-four Japanese patients with R/R AML received once-daily oral gilteritinib in 1 of 6 dose-escalation cohorts (20, 40, 80, 120, 200, and 300 mg/d). Gilteritinib was well tolerated. The MTD was 200 mg/d; dose-limiting toxicities were grade 3 tumor lysis syndrome (120 mg/d; n = 1); and grade 3 elevated blood lactate dehydrogenase, amylase, blood creatine phosphokinase levels, and syncope (all n = 2; 300 mg/d). The RD was 120 mg/d. The most common drug-related grade ≥3 adverse events were thrombocytopenia (n = 4 [16.7%]) and increased blood creatine phosphokinase (n = 3 [12.5%]). Gilteritinib had a dose-proportional PK profile. Among patients with mutated *fms-like tyrosine kinase 3*, the overall response rate (ORR) was 80% (n = 4 of 5; complete remission [CR] with incomplete platelet recovery, 1 [20%]; CR with incomplete hematologic recovery, 2 [40%]; partial remission (PR), 1 [20%]). Among patients with wild-type *fms-like tyrosine kinase 3*, ORR was 36.4%; (n = 4 of 11; CR, 1 [9.1%]; CR with incomplete platelet recovery, 2 [18.2%]; PR, 1 [9.1%]). In

Abbreviations: AE, Adverse event; ALT, Alanine aminotransferase; AML, Acute myeloid leukemia; AST, Aspartate aminotransferase; AUC, Area under the time–concentration curve; AUC_{last}, Area under the time–concentration curve from time 0 to the last measurable concentration; AUC_{tau}, Area under the time–concentration curve for the time between doses; C_{max}, Maximum concentration; CR, Complete remission; CRc, Composite complete remission; CRi, Complete remission with incomplete hematologic recovery; CRM, Continual reassessment method; CRp, Complete remission with incomplete platelet recovery; C_{trough}, Trough concentration; DLT, Dose-limiting toxicity; DNA, Deoxyribonucleic acid; DOR, Duration of response; ECG, Electrocardiogram; FAS, Full analysis set; FLT3, *Fms*-like tyrosine kinase 3; ITD, Internal tandem duplication; MEC, Mitoxantrone, etoposide, and cytarabine; MTD, Maximum tolerated dose; MUGA, Multiple-gate acquisition; NA, Not applicable; NR, No response; ORR, Overall response rate; OS, Overall survival; PK, Pharmacokinetic; PR, Partial remission; QTcF, Corrected QT interval by Fredericia; R/R, Relapsed/refractory; Rac, Accumulation ratio; RD, Recommended dose; SAF, Safety analysis set; SD, Standard deviation; $t_{1/2}$, Half-life; TKD, Tyrosine kinase domain; t_{max}, Time to reach maximum concentration; ULN, Upper limit of normal; US, United States.

conclusion, gilteritinib was well tolerated and demonstrated antileukemic activity in a Japanese R/R AML population.

KEYWORDS
acute myeloid leukemia, bone marrow, *fms*-like tyrosine kinase 3, hematopoiesis, mutation

1 | INTRODUCTION

Fms-like tyrosine kinase 3 (FLT3), expressed on the surface of hematopoietic progenitor cells, plays a critical role in the proliferation, survival and differentiation of multipotent stem cells.[1] Activating mutations in the *FLT3* gene occur in approximately 30% of patients with acute myeloid leukemia (AML) and confer a poor prognosis.[2-4] Two unique activating *FLT3* mutations occur at specific hotspots: internal tandem duplications (*FLT3-ITD*) in the juxtamembrane domain and secondary point mutations in the tyrosine kinase domain (*FLT3-TKD*), most commonly in codon D835.[5,6] As such, *FLT3-ITD* mutations are strong predictors of rapid relapse and short overall survival (OS), whereas secondary *FLT3-TKD* point mutations may confer resistance to FLT3 inhibitors.[4,7-9]

Gilteritinib is a highly specific, potent FLT3/AXL inhibitor with demonstrated activity against FLT3 receptors containing *FLT3-ITD* and *FLT3-TKD D835* mutations.[10,11] Preclinical studies have demonstrated that gilteritinib is a robust inhibitor of FLT3 and AXL, as well as anaplastic lymphoma kinase and leukocyte receptor tyrosine kinase.[11] In leukemic cells, gilteritinib strongly inhibited FLT3 receptors expressing *FLT3-ITD* and *FLT3-TKD D835* mutations, and was a weak inhibitor of FLT3 receptors expressing F691 gatekeeper mutations.[10] AXL, an oncogenic tyrosine kinase that promotes FLT3 activation and may be involved in FLT3 inhibitor resistance, is often overexpressed in patients with AML.[12,13] Because gilteritinib also blocks AXL, which has been shown to suppress the growth of *FLT3-ITD* AML and decrease tumor size, this dual inhibition mechanism may enhance the benefit of gilteritinib in AML.[12,14] Furthermore, gilteritinib has a minimal inhibitory effect on c-Kit, suggesting a lower risk of myelosuppression compared with other tyrosine kinase inhibitors.[11,15] In a recently published phase 1/2 dose-escalation/expansion study of once-daily oral gilteritinib in patients with relapsed/refractory (R/R) AML from the USA, Germany and Italy, gilteritinib was well tolerated with a maximum tolerated dose (MTD) of 300 mg/d.[16] Gilteritinib doses ≥80 mg/d were associated with consistent and potent FLT3 inhibition and strong antileukemic response, with an overall response rate (ORR) of 52% and a median OS duration of 31 weeks.[16]

We conducted a multicenter open-label phase 1 dose-escalation study of gilteritinib in Japanese patients aged ≥18 years with R/R AML. The key objective was to assess the safety and tolerability of gilteritinib with respect to the MTD and determination of the recommended dose (RD) for subsequent studies. Secondary objectives were to evaluate the antileukemic activity and the pharmacokinetic (PK) profile of gilteritinib. This trial is registered as ClinicalTrials.gov identifier NCT02181660.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This was an open-label phase 1 dose-escalation study conducted from 16 June 2014 to 27 June 2016 across 5 centers in Japan. This study was performed according to the ethical principles of the Declaration of Helsinki, Good Clinical Practice guidelines, the principles of informed consent, and the requirements of public registration of clinical trials. The protocol was approved by site-specific institutional review boards. Written informed consent was obtained from each patient at the time of enrolment.

Adults aged ≥18 years with morphologically documented primary or secondary AML (World Health Organization criteria 2008) and an Eastern Cooperative Oncology Group performance status ≤2 were deemed eligible if they were refractory to prior induction therapy or had relapsed after achieving remission with a prior therapy. Patients diagnosed with acute promyelocytic leukemia, *BCR-ABL*–positive leukemia (ie, chronic myelogenous leukemia in blast crisis), or active malignant tumors other than AML or myelodysplastic syndrome were excluded. All inclusion and exclusion criteria are presented in Appendix S1.

2.2 | Procedures

Patients were enrolled into 1 of 6 dose-escalation cohorts: 20, 40, 80, 120, 200, and 300 mg. Initially, at least 1 patient was to be enrolled at a starting dose of 20 mg/d, with at least 3 patients enrolled at each subsequent dose level using the Bayesian continual-reassessment method (CRM; Figure S1).[17]

Patients received an initial dose of oral gilteritinib followed by a 2-day observation period (Cycle 0); beginning on Cycle 1 Day 1, patients followed a repeated dose protocol, receiving oral gilteritinib once a day in a 28-day cycle until a discontinuation criterion was met (Figure 1). Discontinuation criteria included pregnancy (patient or patient's partner), withdrawal of consent, unacceptable adverse events (AEs), failure to achieve partial remission (PR), complete remission (CR), complete remission with incomplete platelet recovery (CRp) or complete remission with incomplete hematologic recovery (CRi) after Cycle 2, and investigator determination that continuation of study treatment would be detrimental to the patient.

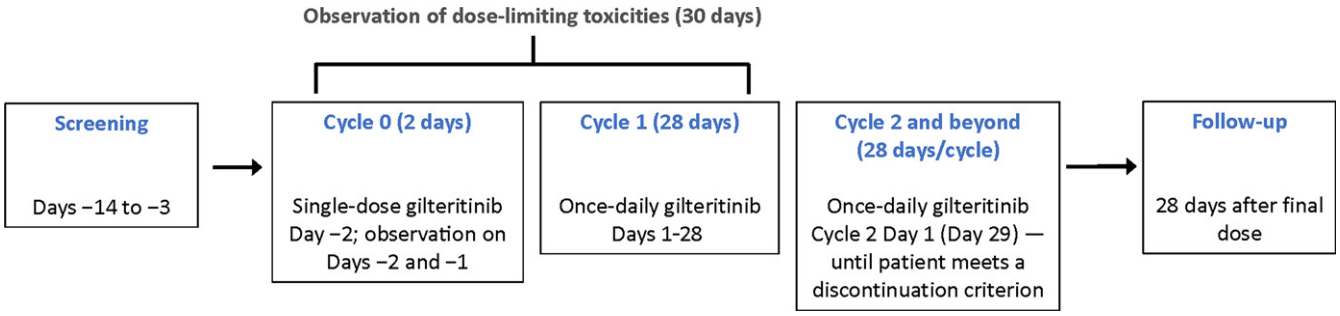

FIGURE 1 Treatment schedule. Each dose level had a single-dose period (Cycle 0, 2 d) and a repeated-dose period (Cycle 1 and subsequent cycles; 28 d/cycle). Patients received a single dose of oral gilteritinib in Cycle 0 Day −2, followed by a 2-d observation period (including the dosing day). From Cycle 1 onwards, patients received once-daily oral gilteritinib in 28-d cycles until a discontinuation criterion was met. The dose-limiting toxicity observation period lasted 30 d from Cycle 0 Day −2 to Cycle 1 Day 28

Dose-limiting toxicities (DLTs) were determined based on safety results from Cycles 0 and 1 in each dose cohort. A DLT was defined as any grade ≥3 nonhematological or extramedullary toxicity that occurred during Cycles 0 or 1 and that was considered by the investigator to be possibly, probably or definitely related to the study drug. Prolonged myelosuppression was considered to be a DLT. Exceptions to the definition of a DLT are noted in Appendix S1.

At the end of Cycle 1 and subsequent cycles, dose escalation was permitted if: (i) no DLT had occurred; (ii) gilteritinib was determined to be tolerable at the next dose level and no dose reductions occurred; or (iii) the patient had requested the dose escalation and escalation was not expected (in the investigator's opinion) to result in any safety concerns. Dose escalation was also permitted if patients did not achieve CR, CRp or CRi after completion of Cycle 1. The MTD and RD were established on the basis of the posterior mean of the DLT rate using the Bayesian CRM and investigator assessment. Criteria for dose reductions and interruptions, treatment discontinuation and MTD determination are outlined in Appendix S1.

2.3 | Assessments and outcomes

Safety and tolerability were assessed by local site-specific monitoring of DLTs and treatment-emergent AEs, changes in physical examinations, vital signs and clinical laboratory investigations. AEs were evaluated in reference to their severity (NCI-CTCAE version 4.0), seriousness, duration and relationship to treatment. Schedules of laboratory investigations and vital sign evaluations are described in Appendix S1.

Antileukemic activity assessment included rates of CR and composite complete remission (CRc; defined as CR plus CRp plus CRi), ORR (defined as CRc plus PR) and duration of response (DOR). Definitions of CR, CRp and CRi were specified according to the International Working Group criteria (Table S1).[18] Duration of response was defined as the period from the first day of achievement of CR, CRp, CRi or PR to the first day of confirmed relapse. Bone marrow aspirates or biopsies were obtained for morphological analysis at screening, Day 28 (±3 days) Cycle 1, Day 1 (±3 days) of all subsequent cycles, and the end of treatment/study discontinuation (±7 days). *FLT3* mutation analyses were performed in bone marrow aspirates or whole blood samples at the time of screening with the patients' consent; samples were evaluated for the presence of *FLT3-ITD* and *FLT3-TKD* point mutations (D835 and I836).

Blood and urine samples were collected at multiple time points after a single dose (until 48 hours) and after multiple doses (until 28 days). Trough PK sampling was performed (Cycle 0: Day −1; Cycle 1: Days 8, 15, 22, 28); PK assays are further described in Appendix S1. Dose proportionality of the maximum concentration (C_{max}) and area under the time–concentration curve (AUC) after a single dose was assessed in the 20-300 mg/d dose groups on Day −2 Cycle 0. Dose proportionality of C_{max} and AUC after multiple doses was assessed in the 20-200 mg/d dose groups on Day 28 Cycle 1. The excretion profile of gilteritinib was assessed in urine samples.

2.4 | Statistical analysis

Sample size was based on a maximum of 6 DLT evaluable subjects per dose level. The safety analysis set (SAF) included all patients who had received at least 1 dose of gilteritinib. The full analysis set (FAS) included all patients who had received at least 1 dose of gilteritinib and who had been assessed for at least 1 efficacy variable after gilteritinib administration. The PK analysis set consisted of patients who had received gilteritinib and who had samples collected for drug concentration analyses at 1 or more time points after gilteritinib administration. Discrete variables were summarized by frequency; summary statistics were calculated for continuous variables. Antileukemic response parameters (ie, CR, CRp, CRi, PR, CRc, and ORR) were summarized by frequency according to dose level in the FAS; median DOR was also determined.

3 | RESULTS

3.1 | Patient disposition and demographic and baseline characteristics

Between 16 June 2014 and 27 June 2016, 27 patients with R/R AML were enrolled across 5 centers in Japan. Of the 27 enrolled

TABLE 1 Demographic and baseline characteristics (safety analysis set; N = 24)

	Gilteritinib dose					
Parameter	**20 mg (n = 1)**	**40 mg (n = 4)**	**80 mg (n = 4)**	**120 mg (n = 4)**	**200 mg (n = 9)**	**300 mg (n = 2)**
Median age, years (range)	67 (NA)	70.5 (66-77)	70.5 (60-81)	74 (71-79)	67 (60-81)	72.5 (70-75)
Median disease duration, months (range)	4.9 (NA)	23.9 (5.5-260.1)	11.3 (10.8-28.2)	6.9 (2.3-9.9)	19.4 (0.8-83.6)	46.2 (32.3-60.2)
Sex, n						
Male	1 (100%)	4 (100%)	2 (50%)	2 (50%)	5 (55.6%)	1 (50%)
Female	0	0	2 (50%)	2 (50%)	4 (44.4%)	1 (50%)
Antecedent hematological disorder, n						
Yes	0	3 (75%)	1 (25%)	0	4 (44.4%)	0
No	1 (100%)	1 (25%)	3 (75%)	4 (100%)	5 (55.6%)	2 (100%)
AML cytogenetic risk status[a], n						
Favorable	0	0	1 (25%)	0	1 (11.1%)	1 (50%)
Intermediate	0	3 (75%)	2 (50%)	2 (50%)	4 (44.4%)	1 (50%)
Unfavorable	0	1 (25%)	1 (25%)	1 (25%)	0	0
FLT3 mutation status[b,c], n						
FLT3 mutation-positive	1 (100%)	1 (25%)	1 (25%)	0	2 (22.2%)	0
FLT3 mutation-negative	0	3 (75%)	2 (50%)	3 (75%)	6 (66.7%)	2 (100%)
FLT3 mutation type[d,c], n						
FLT3-ITD	0	0	1 (25%)	0	2 (22.2%)	0
FLT3-TKD	1 (100%)	1 (25%)	0	0	0	0
Prior AML therapy, n						
Yes	1 (100%)	4 (100%)	4 (100%)	4 (100%)	9 (100%)	2 (100%)
No	0	0	0	0	0	0
Prior AML therapy regimen, n						
7 + 3 standard-dose cytarabine/daunorubicin	0	0	1 (25%)	0	2 (22.2%)	0
7 + 3 standard-dose cytarabine/idarubicin	1 (100%)	1 (25%)	1 (25%)	0	3 (33.3%)	0
7 + 5 standard-dose cytarabine/daunorubicin	0	0	0	1 (25%)	4 (44.4%)	1 (50%)
High-dose cytarabine	0	0	1 (25%)	0	3 (33.3%)	0
Gemtuzumab ozogamicin	0	0	0	0	1 (11.1%)	0
MEC	1 (100%)	1 (25%)	0	1 (25%)	1 (11.1%)	0
Other	1 (100%)	4 (100%)	4 (100%)	4 (100%)	8 (88.9%)	2 (100%)
Prior hematopoietic stem cell transplantation, n						
Yes	0	0	1 (25%)	0	1 (11.1%)	0
No	1 (100%)	4 (100%)	3 (75%)	4 (100%)	8 (88.9%)	2 (100%)

[a]Cytogenetic risk status was missing for 1 patient; 5 patients had other cytogenetic risk status classification.
[b]*FLT3* mutation status was inconclusive for 1 patient and was missing for 2 patients.
[c]*FLT3* mutation status and type were determined by central laboratory testing.
[d]*FLT3* mutation type was missing for 2 patients and was inconclusive for 1 patient.
MEC, mitoxantrone, etoposide, and cytarabine; NA, not applicable.

patients, 3 discontinued before treatment initiation due to voluntary withdrawal (n = 1) and failure to meet inclusion/exclusion criteria (n = 2). Of the remaining 24 patients, all had discontinued treatment during the course of the study for the following reasons: voluntary withdrawal by the patient (n = 2), AE (n = 6), lack of antileukemic response after 2 cycles of therapy (n = 1), progressive disease (n = 14) and change of therapy following a relapse at Cycle 6 (n = 1).

Demographic and baseline characteristics by dose cohort are presented in Table 1. Across the entire study population, most patients were male (n = 15/24 [62.5%]); the median age was 70.5 years (range, 60-81) and the median disease duration was 11.8 months

TABLE 2 Overview of treatment-emergent adverse events (safety analysis set; N = 24)

	Gilteritinib dose					
AEs, n	20 mg (n = 1)	40 mg (n = 4)	80 mg (n = 4)	120 mg (n = 4)	200 mg (n = 9)	300 mg (n = 2)
Any AE	1 (100%)	4 (100%)	4 (100%)	4 (100%)	9 (100%)	2 (100%)
Drug-related AE	1 (100%)	3 (75%)	3 (75%)	4 (100%)	9 (100%)	2 (100%)
Serious AEs	0	1 (25%)	1 (25%)	0	5 (55.6%)	0
Drug-related serious AEs	0	1 (25%)	1 (25%)	0	2 (22.2%)	0
AEs leading to discontinuation of the study drug	0	1 (25%)	1 (25%)	0	2 (22.2%)	2 (100%)
Drug-related AEs leading to discontinuation of the study drug	0	1 (25%)	1 (25%)	0	1 (11.1%)	2 (100%)
Grade ≥3 AEs	1 (100%)	2 (50%)	2 (50%)	2 (50%)	7 (77.8%)	2 (100%)
Drug-related grade ≥3 AEs	0	1 (25%)	1 (25%)	1 (25%)	4 (44.4%)	2 (100%)
Deaths	0	0	1 (25%)[a]	0	0	0

[a]Cause of death was considered to be related to the study drug. Adverse events, AEs.

(range, 0.8-260.1). Of the 5 patients who had *FLT3* mutations, 3 had *FLT3-ITD* mutations and 2 had *FLT3-TKD* mutations. *FLT3* mutation type was inconclusive for 1 patient due to a low sample DNA concentration that did not meet the minimum requirement. *FLT3* mutation status was not available for 2 patients due to lack of patient consent to provide the bone marrow or blood sample (n = 1) and a lapse in bone marrow or blood sample collection (n = 1) for DNA extraction. All patients had received prior chemotherapy for AML, which included 7 + 3 cytarabine/idarubicin (n = 6 [25%]), 7 + 5 cytarabine/daunorubicin (n = 6 [25%]) and other chemotherapy regimens (n = 23; [95.8%]). Furthermore, the majority of patients (n = 22/24 [91.7%]) had not undergone prior hematopoietic stem cell transplantation.

Across the study, the median duration of exposure to gilteritinib was 33.0 days (range, 6.0-166.0); the maximum number of completed treatment cycles was 17. One patient (4.2%) had a dose increase and 2 patients (8.3%) had a dose decrease; dose interruptions occurred in 7 patients (29.2%). One patient in the 80 mg/d dose group who had completed 17 cycles of treatment was excluded from exposure analysis due to compliance issues, given that the actual dates of missed doses were unknown.

3.2 | Safety and tolerability of gilteritinib

Of the 24 patients in the SAF, a total of 3 patients experienced DLTs during Cycle 0 and Cycle 1. One patient in the 120-mg dose group experienced a DLT of grade 3 tumor lysis syndrome. Two patients in the 300-mg dose group experienced DLTs: 1 patient experienced grade 3 elevated blood lactate dehydrogenase level and grade 3 syncope, and the other patient experienced grade 3 elevated amylase and grade 3 elevated blood creatine phosphokinase levels. None of the DLTs were considered to be serious. Based on the posterior mean of the DLT rate as estimated by the Bayesian CRM and investigator opinion, MTD was established at 200 mg/d.

All 24 patients experienced at least 1 AE and most (n = 22/24 [91.7%]) experienced at least 1 treatment-related AE (Table 2). As presented in Table 3, the most common AEs (occurring in ≥20% of patients) were elevated liver enzymes (ie, alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase; n = 9/24 [37.5%]), elevated blood creatine phosphokinase (n = 9/24 [37.5%]), elevated blood lactate dehydrogenase (n = 8/24 [33.3%]), diarrhea (n = 7/24 [29.2%]), pyrexia (n = 7/24 [29.2%]), febrile neutropenia (n = 5/24 [20.8%]), renal impairment (n = 5/24 [20.8%]), hypertension (n = 5/24 [20.8%]) and stomatitis (n = 5/24 [20.8%]). Drug-related AEs occurring in ≥10% of patients were elevated liver enzyme levels (n = 8/24 [33.3%]), elevated blood creatine phosphokinase (n = 7/24 [29.2%]), renal impairment (n = 5/24 [20.8%]), elevated blood lactate dehydrogenase (n = 6/24 [25%]), thrombocytopenia (n = 4/24 [16.7%]), diarrhea (n = 4/24 [16.7%]), stomatitis (n = 4/24 [16.7%]), hypertension (n = 4/24 [16.7%]) and pyrexia (n = 3/24 [12.5%]). The incidences of treatment-related elevated liver enzyme levels, elevated blood creatine phosphokinase level and diarrhea increased with increasing doses of gilteritinib.

Most patients (n = 16/24; 66.7%) experienced grade ≥3 AEs; the most common were thrombocytopenia (n = 4/24 [16.7%]), disseminated intravascular coagulation (n = 3/24; 12.5%), febrile neutropenia (n = 3/24; 12.5%), pneumonia (n = 3/24 [12.5%]) and elevated blood creatine phosphokinase (n = 3/24 [12.5%]). Drug-related grade ≥3 AEs were observed in 9 patients (37.5%). Of these AE, thrombocytopenia (n = 4; 16.7%; 200 and 300 mg/d), increased blood creatine phosphokinase (n = 3; 12.5%; 200 and 300 mg/d), anemia (n = 2; 8.3%; 200 and 300 mg/d), febrile neutropenia (n = 2; 8.3%; 200 and 300 mg/d) and pneumonia (n = 2; 8.3%; 40 and 300 mg/d) occurred in more than 1 patient.

Overall, 7 of 24 patients (29.2%) experienced serious AEs (Tables 2 and 4). Of these, edema, catheter infection, pneumonia, subdural hematoma and febrile neutropenia were considered possibly related to treatment. The only serious AE that occurred in more than 1 patient was subdural hematoma (n = 2/24 [8.3%]; 80 mg/d [n = 1] and 200 mg/d [n = 1]); both cases of subdural hematoma were deemed to be possibly related to the study drug. Both patients with subdural hematoma had low platelet levels that stemmed from the primary disease. One patient, who had received 80 mg/d

TABLE 3 Treatment-emergent adverse events occurring in ≥2 patients by grade (safety analysis set; N = 24)

Adverse events, n	Grade 1-2	Grade 3	Grade 4	Grade 5
Elevated liver enzymes[a]	9 (37.5%)	0	0	0
Elevated blood creatine phosphokinase	6 (25%)	2 (8.3%)	1 (4.2%)	0
Elevated blood lactate dehydrogenase	7 (29.2%)	1 (4.2%)	0	0
Pyrexia	7 (29.2%)	0	0	0
Diarrhea	6 (25%)	1 (4.2%)	0	0
Renal impairment	5 (20.8%)	0	0	0
Hypertension	5 (20.8%)	0	0	0
Stomatitis	5 (20.8%)	0	0	0
Febrile neutropenia	2 (8.3%)	3 (12.5%)	0	0
Corneal erosion	4 (16.7%)	0	0	0
Constipation	4 (16.7%)	0	0	0
Nausea	4 (16.7%)	0	0	0
Headache	4 (16.7%)	0	0	0
Disseminated intravascular coagulation	1 (4.2%)	3 (12.5%)	0	0
Pneumonia	1 (4.2%)	3 (12.5%)	0	0
Thrombocytopenia	0	2 (8.3%)	2 (8.3%)	0
Cough	3 (12.5%)	0	0	0
Pleural effusion	3 (12.5%)	0	0	0
Somnolence	3 (12.5%)	0	0	0
Rash	3 (12.5%)	0	0	0
Hypokalemia	2 (8.3%)	1 (4.2%)	0	0
Dysesthesia	2 (8.3%)	0	0	0
Dysgeusia	2 (8.3%)	0	0	0
Epistaxis	2 (8.3%)	0	0	0
Hypoxia	2 (8.3%)	0	0	0
Hematoma	2 (8.3%)	0	0	0
Hypotension	2 (8.3%)	0	0	0
Anemia	0	2 (8.3%)	0	0
Syncope	0	2 (8.3%)	0	0
Tumor-associated fever	2 (8.3%)	0	0	0
Vomiting	2 (8.3%)	0	0	0
Elevated ALT	2 (8.3%)	0	0	0
Elevated AST	2 (8.3%)	0	0	0
Insomnia	2 (8.3%)	0	0	0
Bone pain	1 (4.2%)	1 (4.2%)	0	0
Subdural hematoma	1 (4.2%)	0	0	1 (4.2%)
Increased amylase	1 (4.2%)	1 (4.2%)	0	0
Sepsis	1 (4.2%)	1 (4.2%)	0	0
Lung infection	1 (4.2%)	1 (4.2%)	0	0
ECG prolonged QT interval	1 (4.2%)	1 (4.2%)	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram.
[a]Ie, elevated ALT, AST, and alkaline phosphatase.

gilteritinib, experienced a fall that impacted the head and was deemed to be the cause of the subdural hematoma that led to the patient's death. The other patient, who had received 200 mg/d gilteritinib, experienced a headache accompanied by hypertension, both of which stemmed from multiple low-grade subdural hematomas that occurred beneath the cerebellar tentorium.

Of 24 patients, 6 (25%) experienced AEs resulting in permanent discontinuation of gilteritinib: pneumonia, 40 mg/d (n = 1) and

TABLE 4 Incidence of serious adverse events (safety analysis set; N = 24)

	Gilteritinib dose					
Serious adverse events, n	20 mg (n = 1)	40 mg (n = 4)	80 mg (n = 4)	120 mg (n = 4)	200 mg (n = 9)	300 mg (n = 2)
Febrile neutropenia	0	0	0	0	1 (11.1%)	0
Cardiomyopathy	0	0	0	0	1 (11.1%)	0
Edema	0	1 (25%)	0	0	0	0
Acute cholangitis	0	0	1 (25%)	0	0	0
Bronchopneumonia	0	0	1 (25%)	0	0	0
Bronchopulmonary aspergillosis	0	0	0	0	1 (11.1%)	0
Pneumonia	0	1 (25%)	0	0	0	0
Sepsis	0	0	1 (25%)	0	0	0
Device-related infection	0	1 (25%)	0	0	0	0
Subdural hematoma	0	0	1 (25%)	0	1 (11.1%)	0
Increased level of fibrin degradation products	0	0	0	0	1 (11.1%)	0

300 mg/d (n = 1); subdural hematoma, 80 mg/d (n = 1); elevated blood creatine phosphokinase, 200 mg/d (n = 1); elevated lactate dehydrogenase, 300 mg/d (n = 1); and delirium, 200 mg/d (n = 1). All AEs leading to treatment discontinuation, except for delirium, were considered drug-related. Pneumonia was the only drug-related AE leading to treatment discontinuation that occurred in more than 1 patient (n = 2/24 [8.3%]).

A prolonged QT interval of >450 ms relative to baseline (using Fridericia's correction factor [QTcF]) was observed in 9 of 24 patients (37.5%) and was identified as an AE in 2 patients (8.3%), 1 of whom received 20 mg/d gilteritinib and the other 40 mg/d gilteritinib. The occurrence of a grade 2 prolonged QTcF interval during treatment Cycles 4 and 5 was deemed possibly related to gilteritinib in the patient who had received the 40 mg/d dose; this patient was subsequently withdrawn from treatment due to the development of pneumonia. A maximum QTcF change of >30 ms was observed in 5 of 22 evaluable patients (22.7%). One patient who received 20 mg/d gilteritinib experienced a maximum postbaseline QTcF of more than 480 ms (mean maximum postbaseline QTcF: 486 ms) and a maximum QTcF change from baseline of >60 ms (maximum postbaseline change: 65 ms).

Due to the increased severity of AEs (all had resolved after interruption of gilteritinib therapy) as well as the observed exposure and response rates in the 200-mg/d dose group, the RD was estimated at 120 mg/d.

3.3 | Antileukemic activity of gilteritinib

A total of 19 patients had at least 1 postbaseline antileukemic response assessment and were included in the FAS; data regarding *FLT3* mutation status were missing or invalid for 3 patients. Of the 16 patients with known *FLT3* mutation status, 5 were *FLT3* mutation-positive and 11 were *FLT3* mutation-negative. Across the FAS dose range, ORR was 47.4% (95% CI: 24.4, 71.1; n = 9/19) (Table 5) with 7 of 19 patients (36.8%; 95% CI: 16.3, 61.6) achieving CRc. The median duration of CRc was 86.5 days (95% CI: 28.0, 116.0); the median duration of remission was 113.5 days (95% CI: 28.0, 139.0).

The ORR and CRc for *FLT3* mutation-positive patients (n = 5) were 80% (95% CI: 28.4, 99.5) and 60% (95% CI: 14.7, 94.7), respectively. The ORR and CRc for patients without *FLT3* mutations (n = 11) were 36.4% (95% CI: 10.9, 69.2) and 27.3% (95% CI: 6.0, 61.0), respectively. Median duration of CRc was similar in *FLT3* mutation-positive patients (63.0 days; 95% CI: 30.0, 116.0) and in patients without *FLT3* mutations (69.5 days; 95% CI: 28.0, 111.0). Median duration of remission was 89.5 days (95% CI: 30.0, not evaluable) in *FLT3* mutation-positive patients and was 111.0 days (95% CI: 28.0, 127.0) in patients without *FLT3* mutations. One *FLT3* mutation-positive patient who completed 17 cycles of gilteritinib (80 mg/d) therapy achieved PR.

3.4 | PK profile of gilteritinib

Mean plasma concentration–time curves for gilteritinib after single and multiple doses are presented in Figure 2. Median t_{max} was reached between 3 and 7 hours after administration of single or multiple doses of gilteritinib (Tables S2 and S3). Single-dose and multiple-dose gilteritinib exposure increased in a dose-proportional manner (Table S4). After multiple dose administration, the mean half-life of gilteritinib was estimated to range from 84 to 126 hours, with an approximate 8-fold accumulation relative to baseline. Mean trough concentrations from Day 1 Cycle 1 through to Day 1 Cycle 2 show achievement of steady-state gilteritinib plasma concentrations by Day 15 Cycle 1 (Figure S2). The mean percentage of unchanged excreted gilteritinib was ≤3.6% after a single dose (data not shown) and ≤13.1% after multiple doses (Table S5).

4 | DISCUSSION

This is the first clinical study of a FLT3 inhibitor in a Japanese R/R AML population. Overall, results from this phase 1 dose-escalation study of gilteritinib demonstrate that gilteritinib was well tolerated

TABLE 5 Clinical response to gilteritinib (full analysis set; N = 19)

Response parameter, n (%, [95% CI])[a]	All patients (N = 19)[b]						*FLT3* mutation-positive patients[c] (n = 5)				*FLT3* mutation-negative patients[b] (n = 11)
	20 mg (n = 1)	40 mg (n = 3)	80 mg (n = 4)	120 mg (n = 2)	200 mg (n = 7)	300 mg (n = 2)	20 mg (n = 1)	40 mg (n = 1)	80 mg (n = 1)	200 mg (n = 2)	Total (n = 11)
CR	0	0	1 (25 [0.6, 80.6])	0	0	0	0	0	0	0	1 (9.1 [0.2, 41.3])
CRp	0	0	0	0	3 (42.9 [9.9, 81.6])	0	0	0	0	1 (50 [1.3, 98.7])	2 (18.2 [2.3, 51.8])
CRi	1 (100 [2.5, 100])	0	0	1 (50 [1.3, 98.7])	1 (14.3 [0.4, 57.9])	0	1 (100 [2.5, 100])	0	0	1 (50 [1.3, 98.7])	0
PR	0	1 (33.3 [0.8, 90.6])	1 (25 [0.6, 80.6])	0	0	0	0	0	1 (100 [2.5, 100])	0	1 (9.1 [0.2, 41.3])
CRc	1 (100 [2.5, 100])	0	1 (25 [0.6, 80.6])	1 (50 [1.3, 98.7])	4 (57.1 [18.4, 90.1])	0	1 (100 [2.5, 100])	0	0	2 (100 [15.8, 100])	3 (27.3 [6.0, 61.0])
ORR	1 (100 [2.5, 100])	1 (33.3 [0.8, 90.6])	2 (50 [6.8, 93.2])	1 (50 [1.3, 98.7])	4 (57.1 [18.4, 90.1])	0	1 (100 [2.5, 100])	0	1 (100 [2.5, 100])	2 (100 [15.8, 100])	4 (36.4 [10.9, 69.2])

CI, confidence interval; CR, complete remission; CRc, composite complete remission (CR plus CRp plus CRi); CRi, complete remission with incomplete hematological recovery; CRp, complete remission with incomplete platelet recovery; ORR, overall response rate; PR, partial remission.
Response was defined as CRc plus PR.
[a]Exact 95% CI was established using the binomial distribution.
[b]Of all patients in the full analysis set, data regarding *FLT3* mutation status were missing for 2 patients and were invalid for 1 patient.
[c]*FLT3* mutation status was determined by a central laboratory.

FIGURE 2 Mean plasma concentration–time profile after single and multiple doses of gilteritinib. A, Mean plasma concentration–time profile of gilteritinib after administration of a single dose on Day −2 Cycle 0. Plasma concentration is depicted on a semi-logarithmic scale. B, Mean plasma concentration–time profile of gilteritinib after administration of multiple repeating doses of gilteritinib on Day 28 Cycle 1. Plasma concentration is depicted on a semi-logarithmic scale

at doses of up to 200 mg/d, which was deemed to be the MTD. Based on the observed exposure, clinical response and safety profiles of gilteritinib in this study, a starting dose of 120 mg/d was expected to provide sufficient drug exposure required for clinical efficacy in subsequent studies. Gilteritinib exhibited a linear dose-proportional PK profile at doses ranging from 20 to 300 mg/d. Across the dose range (20-200 mg/d), ORR and CRc were 47.4% and 36.8%, respectively; CRc rates were 60% in *FLT3* mutation-positive patients and 27.3% in *FLT3* mutation-negative patients. The median duration of CRc was similar in *FLT3* mutation-positive and *FLT3* mutation-negative patients. One *FLT3* mutation-positive patient who received 17 cycles of gilteritinib therapy achieved PR.

Although the MTD reported for gilteritinib in the current study (200 mg/d) is lower than that reported in the phase 1/2 study (300 mg/d), there was no difference in the incidence of DLTs at the 300-mg/d level or the PK profile of gilteritinib between the Japanese and the US/European R/R AML populations.[16] Moreover, the sample

size (N = 24) is much smaller than that in the phase 1/2 study (N = 252), which allows for greater variability.[16]

Mutational variations between the Japanese AML population and the US/European AML population have been observed. Among patients enrolled in the JALSG AML201 study, *FLT3* was the most commonly mutated gene, with mutations occurring in approximately 25% of patients,[19] which was comparable to the US/European AML population (28%).[2] The incidence of *DNA methyltransferase 3 alpha* (*DNMT3A*) mutations (approximately 16%)[19] was lower than that observed in the US/European AML population (26%)[2] and the incidences of *CCAAT/enhancer-binding protein alpha* (*CEBPA*) and *c-Kit* mutations (approximately 16% and 14%, respectively)[19] were higher in the JALSG AML201 study population than in the US/European AML population (6% and 4%, respectively).[2] The higher number of patients with *c-Kit* mutations could be attributed to the increased occurrence of core-binding factor AML in the JALSG AML201 study population.[19] Despite these potential mutational differences, the reported outcomes after treatment with gilteritinib in Japanese patients with R/R AML in the current study were generally similar to those reported in the larger phase 1/2 US/European R/R AML study population.

Several multikinase and FLT3 inhibitors have been evaluated in patients with AML. As a single agent, the multikinase inhibitor midostaurin reduced peripheral blast counts in both patients with mutated and wild-type *FLT3* AML;[20] however, bone marrow blast reductions were limited, clinical response duration was brief (50-56 days) and CR was not achieved.[20] In patients aged <60 years, the 3-year event-free survival rate after treatment with sorafenib plus intensive chemotherapy (40%) was greater than that observed in the placebo arm (22%). However, no improvement in OS and a higher incidence of grade ≥3 AEs was observed in the sorafenib arm.[21] In patients aged >60 years, sorafenib plus intensive chemotherapy did not improve CR rates or event-free survival and OS.[22]

Of the FLT3 inhibitors in development, quizartinib is associated with high response rates in patients with R/R AML; however, durable survival necessitated allogeneic HSCT.[23] Treatment resistance, attributable to the development of treatment-emergent *FLT3-TKD* mutations, was frequently observed in nontransplanted patients.[24] Moreover, prolongation of the QTc interval was observed at doses of 200 and 300 mg,[25] and inhibition of c-Kit by quizartinib was associated with myelosuppression.[15,26] In patients with *FLT3* mutation-positive R/R AML, crenolanib showed strong antileukemic activity; however, CR/CRi rates were low; nausea, vomiting and hepatotoxic AEs were frequently observed.[27,28]

In this study, elevated liver enzyme levels observed in one-third of patients with R/R AML were associated with gilteritinib therapy; however, all cases were less than grade 3 in severity. Hepatotoxicity was also associated with sorafenib and crenolanib therapy in patients with *FLT3* mutation-positive AML.[28,29] Among other common AEs related to gilteritinib therapy reported in the current study, elevated blood creatine phosphate levels and elevated blood lactate dehydrogenase levels were identified as DLTs in only 2 patients, both of whom had received gilteritinib doses of 300 mg/d. Furthermore, the occurrence of a possible treatment-related prolongation of the QTcF interval was observed in only 1 patient (4.2%) in the 40 mg/d dose cohort.

As with other small-scale nonrandomized nonblinded phase 1 studies, evaluation of gilteritinib in an ethnically homogeneous patient population restricts extrapolation of these results to the larger R/R AML population. The short follow-up period (28 days) did not allow for assessment of long-term safety, durability of response and long-term survival. Unlike the *FLT3* mutation-enriched R/R AML population in the phase 1/2 study,[16] most patients (approximately 67%) in our study were *FLT3* mutation negative. Despite these limitations, no significant differences in response rate, safety or PK profiles of gilteritinib were observed between our study and the phase 1/2 study.[16] Furthermore, the demonstrated activity of gilteritinib against *FLT3-TKD* mutations suggest a potential benefit in treatment-resistant *FLT3* mutation-positive AML.[10,11]

In conclusion, gilteritinib was well tolerated and induced antileukemic responses in a Japanese R/R AML patient population that were comparable to those observed in *FLT3* mutation-enriched US/European patients with R/R AML.[16] Response rates with gilteritinib monotherapy were higher than those reported for other FLT3 inhibitors.[23,25,27,28] Our data further demonstrate the utility of gilteritinib as a single agent in the treatment of R/R AML. With no currently approved treatment for *FLT3* mutation-positive R/R AML in Japan, gilteritinib is a promising therapeutic agent.

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CONFLICT OF INTEREST

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REFERENCES

1. Gilliland DG, Griffin JD. The roles of FLT3 in hematopoiesis and leukemia. *Blood*. 2002;100:1532-1542.
2. Cancer Genome Atlas Research Network. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. *N Engl J Med*. 2013;368:2059-2074.
3. Levis M. FLT3 mutations in acute myeloid leukemia: what is the best approach in 2013? *Hematol Am Soc Hematol Educ Program*. 2013;2013:220-226.
4. Thiede C, Steudel C, Mohr B, et al. Analysis of FLT3-activating mutations in 979 patients with acute myelogenous leukemia: association with FAB subtypes and identification of subgroups with poor prognosis. *Blood*. 2002;99:4326-4335.
5. Nakao M, Yokota S, Iwai T, et al. Internal tandem duplication of the flt3 gene found in acute myeloid leukemia. *Leukemia*. 1996;10:1911-1918.
6. Yamamoto Y, Kiyoi H, Nakano Y, et al. Activating mutation of D835 within the activation loop of FLT3 in human hematologic malignancies. *Blood*. 2001;97:2434-2439.
7. Alvarado Y, Kantarjian HM, Luthra R, et al. Treatment with FLT3 inhibitor in patients with FLT3-mutated acute myeloid leukemia is associated with development of secondary FLT3-tyrosine kinase domain mutations. *Cancer*. 2014;120:2142-2149.
8. Smith CC, Wang Q, Chin CS, et al. Validation of ITD mutations in FLT3 as a therapeutic target in human acute myeloid leukaemia. *Nature*. 2012;485:260-263.
9. Man CH, Fung TK, Ho C, et al. Sorafenib treatment of FLT3-ITD(+) acute myeloid leukemia: favorable initial outcome and mechanisms of subsequent nonresponsiveness associated with the emergence of a D835 mutation. *Blood*. 2012;119:5133-5143.
10. Lee LY, Hernandez D, Rajkhowa T, et al. Pre-clinical studies of gilteritinib, a next-generation FLT3 inhibitor. *Blood*. 2017;129:257-260.
11. Mori M, Kaneko N, Ueno Y, et al. Gilteritinib, a FLT3/AXL inhibitor, shows antileukemic activity in mouse models of FLT3 mutated acute myeloid leukemia. *Invest New Drugs*. 2017;35:556-565.
12. Park IK, Mishra A, Chandler J, Whitman SP, Marcucci G, Caligiuri MA. Inhibition of the receptor tyrosine kinase Axl impedes activation of the FLT3 internal tandem duplication in human acute myeloid leukemia: implications for Axl as a potential therapeutic target. *Blood*. 2013;121:2064-2073.
13. Park IK, Mundy-Bosse B, Whitman SP, et al. Receptor tyrosine kinase Axl is required for resistance of leukemic cells to FLT3-targeted therapy in acute myeloid leukemia. *Leukemia*. 2015;29:2382-2389.
14. Ben-Batalla I, Schultze A, Wroblewski M, et al. Axl, a prognostic and therapeutic target in acute myeloid leukemia mediates paracrine crosstalk of leukemia cells with bone marrow stroma. *Blood*. 2013;122:2443-2452.
15. Galanis A, Levis M. Inhibition of c-Kit by tyrosine kinase inhibitors. *Haematologica*. 2015;100:e77-e79.
16. Perl AE, Altman JK, Cortes J, et al. Selective inhibition of FLT3 by gilteritinib in relapsed or refractory acute myeloid leukaemia: a multicentre, first-in-human, open-label, phase 1-2 study. *Lancet Oncol*. 2017;18:1061-1075.
17. O'Quigley J, Pepe M, Fisher L. Continual reassessment method: a practical design for phase 1 clinical trials in cancer. *Biometrics*. 1990;46:33-48.
18. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol*. 2003;21:4642-4649.
19. Kihara R, Nagata Y, Kiyoi H, et al. Comprehensive analysis of genetic alterations and their prognostic impacts in adult acute myeloid leukemia patients. *Leukemia*. 2014;28:1586-1595.
20. Fischer T, Stone RM, Deangelo DJ, et al. Phase IIB trial of oral Midostaurin (PKC412), the FMS-like tyrosine kinase 3 receptor (FLT3) and multi-targeted kinase inhibitor, in patients with acute myeloid leukemia and high-risk myelodysplastic syndrome with either wild-type or mutated FLT3. *J Clin Oncol*. 2010;28:4339-4345.
21. Röllig C, Serve H, Huttmann A, et al. Addition of sorafenib versus placebo to standard therapy in patients aged 60 years or younger with newly diagnosed acute myeloid leukaemia (SORAML): a multicentre, phase 2, randomised controlled trial. *Lancet Oncol*. 2015;16:1691-1699.
22. Serve H, Krug U, Wagner R, et al. Sorafenib in combination with intensive chemotherapy in elderly patients with acute myeloid leukemia: results from a randomized, placebo-controlled trial. *J Clin Oncol*. 2013;31:3110-3118.
23. Levis MJ, Martinelli G, Perl AE, et al. The benefit of treatment with quizartinib and subsequent bridging to HSCT for FLT3-ITD(+) patients with AML. *J Clin Oncol*. 2014;32.
24. Wander SA, Levis MJ, Fathi AT. The evolving role of FLT3 inhibitors in acute myeloid leukemia: quizartinib and beyond. *Ther Adv Hematol*. 2014;5:65-77.
25. Cortes JE, Kantarjian H, Foran JM, et al. Phase I study of quizartinib administered daily to patients with relapsed or refractory acute myeloid leukemia irrespective of FMS-like tyrosine kinase 3-internal tandem duplication status. *J Clin Oncol*. 2013;31:3681-3687.
26. Levis MJ, Perl AE, Dombret H, et al. Final results of a phase 2 open-label, monotherapy efficacy and safety study of quizartinib (AC220) in patients with FLT3-ITD positive or negative relapsed/refractory acute myeloid leukemia after second-line chemotherapy or hematopoietic stem cell transplantation. *Blood*. 2012;120:673.
27. Randhawa J, Kantarjian HM, Borthakur G, et al. Results of a phase II study of crenolanib in relapsed/refractory acute myeloid leukemia patients (Pts) with activating FLT3 mutations. *Blood*. 2014;124. abstract 389.
28. Cortes JE, Kantarjian HM, Kadia TM, et al. Crenolanib besylate, a type I pan-FLT3 inhibitor, to demonstrate clinical activity in multiply relapsed FLT3-ITD and D835 AML. *J Clin Oncol*. 2016;34.
29. Metzelder SK, Schroeder T, Finck A, et al. High activity of sorafenib in FLT3-ITD-positive acute myeloid leukemia synergizes with allo-immune effects to induce sustained responses. *Leukemia*. 2012;26:2353-2359.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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