A Phase 1 Study of Gilteritinib in Combination With Induction and Consolidation Chemotherapy in Patients With Newly Diagnosed Acute Myeloid Leukemia: Final Study Results

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INTRODUCTION

- FMS-like tyrosine kinase 3 (*FLT3*) is the most commonly mutated gene in acute myeloid leukemia (AML), occurring in approximately 30% of patients[1]
- *FLT3* internal tandem duplication (*FLT3*-ITD) and point mutations within the tyrosine kinase domain lead to constitutive tyrosine kinase activity, and are associated with an increased risk of relapse, a shorter time to relapse, and poorer overall survival (OS)[1]
- Gilteritinib was the first FLT3 inhibitor to be approved as a monotherapy in patients with relapsed/refractory (R/R) AML and mutated *FLT3*; it has been shown to consistently inhibit FLT3 in patients[2], and in the phase 3 ADMIRAL study was seen to confer a longer survival and greater chance of remission than salvage chemotherapy[3]

Objective

This phase 1 study aimed to assess the safety and tolerability of gilteritinib given in combination with intensive chemotherapy, as well as its efficacy, in patients with newly diagnosed AML

METHODS

Study design

- Patients were enrolled into one of four parts of this multi-center, open-label study (NCT02236013)
- Part 1, **Gilteritinib Dose Escalation**, aimed to determine the maximum tolerated dose (MTD), and comprised three distinct periods:
  - remission induction: 3 days of idarubicin and 7 days of cytrabine (3 + 7), plus gilteritinib for 14 days, D4–D17 (doses: 20 mg, 40 mg, 80 mg, 120 mg, and 200 mg), up to 2 cycles
  - consolidation: high-dose cytrabine, plus gilteritinib for 14 days, D1–D14 (at the dose that participants received during induction), up to 3 cycles
  - maintenance: gilteritinib for 28 days, D1–D28, up to a total of 26 cycles
- Part 2, **Dose Expansion:** participants received gilteritinib at MTD (120 mg/day) and followed the same treatment cycle as part 1
- Part 3, **Alternative Anthracycline and Schedule:** the gilteritinib dosing schedule during induction was modified to begin after the 7 + 3 chemotherapy regimen (D8–D21), and patients were split into two cohorts: 3 + 7 idarubicin and cytrabine (as for part 1 and 2), and 3 + 7 daunorubicin and cytrabine. Consolidation and maintenance proceeded as for part 1
- Part 4, **Continuous Gilteritinib Exposure during Consolidation:** patients followed the same treatment cycle as the Part 3 daunorubicin cohort, except that during consolidation, gilteritinib was administered up to 56 consecutive days

Key inclusion/exclusion criteria

- Key inclusion criteria: ≥18 years of age; newly diagnosed AML; Eastern Cooperative Oncology performance status of ≤2; meet protocol-specified criteria on clinical laboratory tests. *FLT3*$^{mut+}$ was not a requirement
- Key exclusion criteria: diagnosis of acute promyelocytic leukemia or AML with good risk cytogenetics; BCR-ABL-positive leukemia, or active malignant tumors other than AML or myelodysplastic syndrome

RESULTS

1. Study patients and baseline characteristics

- Of the 103 participants screened, 80 were allocated treatment, with 79 receiving study drug and 78 receiving gilteritinib. The participants comprised the safety analysis set: 33 in part 2, 14 in part 3, and 12 in part 4
- Overall, 62.8% of participants were male, the median age was 59.0 years (range: 23 to 77), and the median body mass index was 28.4 (18.1, 48.1) (**Table 1**)
- Median follow-up was 37.7 months. 27 (33.8%) participants received a hematopoietic stem cell transplant (HSCT) during or at the end of treatment

2. Safety and tolerability

- MTD was found to be 120 mg/d, and dose-limiting toxicities occurred in 15/78 (19.2%) patients
- Across the study, adverse events (AEs) led to gilteritinib discontinuation in 24.4% of patients (**Table 2**),
- Overall, 93.6% of participants experienced at least 1 Grade ≥ 3 treatment-related AE (**Table 3**). The most common Grade ≥ 3 treatment-related AEs were febrile neutropenia (66.7%), platelet count decrease (23.1%), and white blood cell decrease (21.8%) (**Table 3**)

Table 1. Baseline characteristics and *FLT3* mutation status (safety analysis set)

Characteristics	N=78
Male, male, n (%)	49 (62.8)
Age, median (range), y	59.0 (23 to 77)
BMI, median (range), kg/m²	28.4 (18.1 to 48.1)
BSA, median (range), m²	2.0 (1.1 to 2.8)
***FLT3* mutation status, n (%)**	
FLT3^{mut+}	44 (56.4)
FLT3-ITD+	33 (42.3)
FLT3^{WT}	32 (41.0)
Unknown	2 (2.6)

Data are presented from all patients who received gilteritinib.
Abbreviations: BMI, body mass index; BSA, body surface area; *FLT3*, FMS-like tyrosine kinase 3; ITD, internal tandem duplication.

3. Antileukemic response

- At the end of treatment, composite complete remission (CRc: complete remission [CR] + CR with incomplete hematologic recovery [CRi] + CR with incomplete platelet recovery [CRp]), CR, CRi, and CRp were 79.7%, 54.4%, 21.5%, and 3.8%, respectively, in the overall population; for *FLT3*$^{mut+}$ patients, CRc, CR, CRi, and CRp rates were 90.9%, 70.5%, 13.6%, and 6.8%, respectively
- While censoring at HSCT, the median (95% confidence interval [CI]) disease-free survival (DFS) for all participants with non-missing values (n=63; 23 events, 40 censored) was 460 days (288, 970). For *FLT3*$^{mut+}$ participants (n=40; 11 events, 29 censored) median DFS was 460 (150, 970) days, whereas in *FLT3*-negative participants (n=22; 11 events, 11 censored), the median DFS was 288 (23, 971) days
- In the overall population (n=69; 32 events, 37 censored) receiving ≥80 mg/d gilteritinib, median (95% CI) OS was 1176 (661, not estimable [NE]). For *FLT3*$^{mut+}$ participants (n=41; 18 events, 23 censored) and *FLT3*-negative participants (n=26; 13 events, 13 censored), median OS was 1397 (936, NE) days and 998 (392, NE) days, respectively. For *FLT3*$^{mut+}$ participants, survival probabilities for 26 weeks, 1 year and 2 years were 92.4%, 82.1% and 69.2%, respectively; probabilities for *FLT3*-negative participants were 79.2%, 75.0%, and 53.8% (Figure 1)
- Anthracycline choice did not substantially impact CRc rate or toxicity
- In patients who achieved CRc with gilteritinib ≥120 mg/d, mutational clearance of *FLT3*-ITD (summed *FLT3*-ITD:total *FLT3* ratio ≤10^{-4}) after consolidation was 84.6% (11/13) (**Table 4**)

Table 4. *FLT3*-ITD clearance in subjects who achieved CRc with ≥120 mg gilteritinib

MRD status	End of induction (N=12)	Beginning of consolidation (N=8)	After consolidation (N=13)
MRD negative	4 (33.3%)	3 (37.5%)	11 (84.6%)
MRD positive	8 (66.7%)	5 (62.5%)	2 (15.4%)

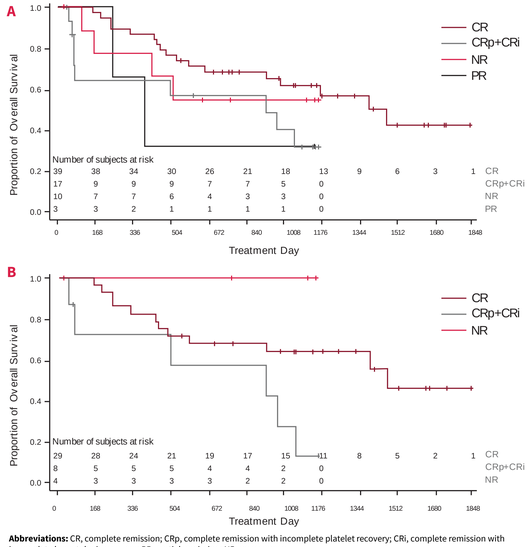
FLT3-ITD signal ratio was defined as the *FLT3*-ITD to total *FLT3* frequency. MRD negative is defined as summed *FLT3*-ITD signal ratio of any post-baseline sample <10^{-4}. If a subject has multiple MRD samples collected across different timepoints, the MRD status is negative if at least one MRD sample is negative and MRD status is positive if all available MRD samples are positive.
Abbreviations: CRc, composite complete remission; *FLT3*, FMS-like tyrosine kinase 3; ITD, internal tandem duplication; MRD, minimal residual disease

Table 2. Overview of treatment-emergent adverse events

Adverse events, n (%)	All (N=78)	Treatment related (N=78)
All AEs	78 (100)	69 (88.5)
AEs leading to death	2 (2.6)	0
SAEs	77 (98.7)	62 (79.5)
AEs leading to permanent discontinuation	19 (24.4)	11 (14.1)

Drug/regimen-related events were possibly or probably related, as assessed by the investigator, or records where the relationship was missing.
Abbreviations: AE, adverse event; SAE, serious adverse event

Figure 1. Kaplan-Meier plot of overall survival in gilteritinib ≥80 mg/day dose: (A) overall population; (B) *FLT3*$^{mut+}$ participants



Abbreviations: CR, complete remission; CRp, complete remission with incomplete platelet recovery; CRi, complete remission with incomplete hematologic recovery; PR, partial remission; NR, no response

Table 3. Grade 3 or higher treatment-emergent adverse events occurring in ≥ 10% of patients

AEs, n (%)	Total (N=78)
Any AE grade ≥3	73 (93.6)
Febrile neutropenia	52 (66.7)
Platelet count decreases	18 (23.1)
Neutrophil count decreased	17 (21.8)
White blood cell count decreased	17 (21.8)
Thrombocytopenia	16 (20.5)
Neutropenia	14 (17.9)
Anemia	12 (15.4)
Pneumonia	12 (15.4)
ALT increased	11 (14.1)
Bacteremia	9 (11.5)
Sepsis	9 (11.5)

Abbreviations: AE, adverse event; ALT, alanine aminotransferase

CONCLUSIONS

- Gilteritinib in combination with induction and consolidation chemotherapy was well-tolerated in patients with ND AML, in both the overall population and those with *FLT3*$^{mut+}$
- Favorable antileukemic responses were observed in terms of CR and OS, particularly in the *FLT3*$^{mut+}$ population
- A high rate of mutational clearance was observed among patients with *FLT3*-ITD mutations who received a dose of 120 mg, and achieved CRc
- These results support ongoing randomized trials testing this approach against current standards.

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