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Gilteritinib plus azacitidine in patients with newly diagnosed *FLT3* mutation-positive acute myeloid leukemia who were ineligible for intensive chemotherapy: final results of the phase III LACEWING study

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Data Sharing Statement

Details for how researchers may request access to anonymized participant-level data, trial-level data and protocols from Astellas-sponsored clinical trials can be found at https://www.clinicaltrials.astellas.com/transparency/.

Clinical Trial Registration

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ABSTRACT

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The phase 3, open-label LACEWING study evaluated efficacy and safety of the FMS-like tyrosine kinase 3 (FLT3) inhibitor gilteritinib (GIL) plus azacitidine (AZA) in newly diagnosed (ND) *FLT3*-mutated (*FLT3*$^{mut+}$) acute myeloid leukemia (AML) ineligible for intensive induction chemotherapy (IIC). Patients were enrolled into a safety cohort (n=15) or randomized (n=168) to GIL+AZA, GIL, or AZA. We present final (6.5-year) outcomes and additional data on mutational subgroups, measurable residual disease (MRD), and pharmacokinetics. Median overall survival (OS) was 9.82 versus 9.23 months (GIL+AZA vs AZA, p=0.182) and 5.24 months (GIL). Corresponding two-year OS rates were 18.8%, 12.9%, and 4.5%. Overall response rates were 70.2% versus 36.8% (GIL+AZA vs AZA, nominal p<0.001) and 72.7% (GIL). Among patients achieving remission, MRD negativity was 30.9%, 30.8%, and 44.4%. Treatment-related adverse event incidence was 12.8, 14.6, and 9.1 events/patient-year. Exploratory analyses demonstrated longer median OS following GIL+AZA versus AZA in patients with *FLT3* internal tandem duplications (ITD) without tyrosine kinase domain mutations (11.63 vs 8.87 months, nominal p=0.047), patients with high *FLT3*-ITD allelic ratio (11.89 vs 7.46 months, nominal p=0.016), and propensity score matched patients without subsequent AML therapy (9.00 vs 3.32 months). Patients with *NPM1*-mutated AML with/without *DMNT3A* mutations exhibited trends toward improved OS with GIL+AZA. New *RAS/MAPK* mutations were identified in 39% of GIL+AZA/GIL patients at relapse. Mean GIL trough concentrations at cycle-1-day-15 for GIL+AZA and GIL were 744 and 650 ng/mL. Although median OS was not significantly different between GIL+AZA and AZA, these results provide valuable insights informing future GIL-based combinations.

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INTRODUCTION

Currently, the optimal upfront chemotherapy regimen for older adults with newly diagnosed (ND) FMS-like tyrosine kinase 3-mutated (*FLT3*$^{mut+}$) acute myeloid leukemia (AML) who are ineligible for intensive induction chemotherapy is uncertain.[1,2] Azacitidine (AZA), a hypomethylating agent, is well tolerated as an alternative induction therapy for individuals with ND AML agnostic of mutation status, but has shown limited effectiveness as upfront therapy in patients with *FLT3*$^{mut+}$ AML ineligible for intensive induction chemotherapy.[3] Moreover, the benefit of venetoclax plus AZA seems limited in this molecular subset.[4,5] Consequently, alternative therapies to intensive chemotherapy for this specific patient population are of clinical interest.

The small-molecule FLT3 inhibitor gilteritinib (GIL) has been approved for the treatment of adult patients with *FLT3*$^{mut+}$ relapsed/refractory (R/R) AML[6] based on the phase 3 ADMIRAL trial, which demonstrated improved antileukemic efficacy for GIL versus salvage chemotherapy.[7,8] GIL targets FLT3 receptors carrying either internal tandem duplication (ITD) and/or tyrosine kinase domain (TKD) mutations at 50% lower inhibitory concentrations than the wild-type receptor; this includes TKD mutations affecting the D835 residue, a key mechanism of resistance to other FLT3 inhibitors such as quizartinib and sorafenib.[9-12] Furthermore, previous studies using xenografted mouse models identified a synergistic relationship between GIL and AZA, resulting in improved efficacy for combination therapy versus GIL or AZA monotherapy.[13] The main objective of the LACEWING study was to determine the efficacy of GIL+AZA versus AZA monotherapy, as measured by overall survival (OS), in patients with ND *FLT3*$^{mut+}$ AML ineligible for intensive induction chemotherapy. Additional objectives were to compare event-free survival (EFS), response rates, safety, patient-reported outcomes (PRO), GIL pharmacokinetics (PK), and AML mutations prior to and following therapy with GIL+AZA, GIL monotherapy, and AZA monotherapy.

Although interim findings from LACEWING (at a study duration of 4 years and 9 months) were previously published,[14] here we present the final study analyses after 6.5 years of duration. These results include outcomes following GIL monotherapy and analyses of measurable residual disease (MRD), PK, and PRO. Of note, this trial was conducted before the publication of the VIALE-A phase 3 clinical trial results, which established venetoclax and AZA over AZA monotherapy for upfront therapy of older and/or patients with AML who are ineligible for intensive chemotherapy.[3]

METHODS

Ethics Approval and Patient Consent

The study was conducted in accordance with International Council for Harmonisation guidelines for Good Clinical Practice and the Declaration of Helsinki, and applicable regulations/guidelines governing clinical study conduct and ethical principles. The protocol, protocol amendments, and other relevant documentation were submitted for approval to the relevant Institutional Review Board or Independent Ethics Committee at each study site prior to study initiation. Authors had access to data used for manuscript preparation and developed and approved the manuscript, with writing/editorial support funded by the trial sponsor. Written informed consent was obtained from each patient before study entry.

Study Design

This randomized, open-label, phase 3 study (NCT02752035) was conducted in the United States, Canada, Belgium, France, Spain, Italy, Poland, Germany, Australia, Japan, Republic of Korea, and Taiwan between December 2, 2015 (first informed consent), and May 31, 2022 (cutoff date for present analyses) across 77 centers. The study design was previously described (**Figure S1**).[14]

Prior to initiation of the randomized cohort, 15 patients were enrolled in a separate safety cohort to assess the safety and tolerability of GIL+AZA in dose-escalation groups receiving 80 and 120 mg GIL.

In the randomized cohort, patients were stratified based on age: <75 or ≥75 years. Based on data from the safety cohort, a GIL starting dose of 120 mg once daily, orally and continuously for 28-day cycles, was used for the randomized cohort. AZA at 75 mg/m^2/day was administered subcutaneously/intravenously on days 1–7 of each cycle. In the initial study design, patients were randomized in a 1:1:1 ratio to receive GIL+AZA, GIL, or AZA. The GIL arm was discontinued on September 5, 2018, approximately 12 months after initiation of the randomized cohort, due to increased use of AZA in clinical practice and the efficacy of GIL+AZA observed in the safety cohort. Twenty-two patients enrolled in this arm continued GIL until unacceptable toxicity, loss of clinical benefit, or another treatment discontinuation criterion. In a revised study design, patients were randomized in a 2:1 ratio to either GIL+AZA or AZA. Dose interruptions, reductions, and escalations after the first cycle were permitted per prespecified criteria.[14] Patients continued treatment until lack of clinical benefit per the investigator, unacceptable toxicity, or meeting discontinuation criteria.[14]

Patients

Eligibility criteria have been published previously.[14] Briefly, enrolled patients were adults ≥18 years with ND, untreated AML characterized by centrally confirmed *FLT3*-ITD and/or *FLT3*-TKD D835/I836 mutations, determined using the LeukoStrat CDx *FLT3* Mutation Assay (Invivoscribe, San Diego, CA, USA). Patients were also deemed ineligible for intensive induction chemotherapy (**Supplementary Methods**). Patients with *FLT3*-ITD mutations were classified based on low (<0.5) or high (≥0.5) allelic ratio (AR), calculated as the ratio of the peak height of the mutant polymerase chain reaction (PCR) product to the peak height of the wild-type PCR product, assessed by capillary electrophoresis.

Endpoints

The primary endpoint was OS, defined as time from randomization until death from any cause, or otherwise censored at last contact. Secondary endpoints included EFS, defined as time from randomization until date of documented relapse from complete remission (CR), treatment failure, or death from any cause, whichever occurred first; response rates; remission rates and duration of remission; and safety/tolerability. The event time for treatment failure was 1 day (0.03 months). Definitions of response parameters are provided in **Table S1**. Exploratory endpoints included PK, MRD via next-generation sequencing of *FLT3*, *FLT3* mutation status (at baseline/screening and relapse) and a panel of genes commonly mutated in AML, and PRO (**Supplementary Methods**).

Assessments for each endpoint have been described previously[14] and are listed in the **Supplementary Methods**. Statistical methods, including power calculations, have been described previously.[14]

RESULTS

Patients

Of 870 patients screened, 15 enrolled in the safety cohort and 168 enrolled in the randomized cohort by December 2020, when the study sponsor terminated enrollment based on the protocol-specified boundary for futility. Most (601/687, 87.5%) screening failures were due to lack of *FLT3* mutations. In the safety cohort, 9 patients received GIL 80 mg daily and 6 received GIL 120 mg daily. In the randomized cohort, 88, 54, and 22 patients received GIL+AZA, AZA, and GIL, respectively (**Figure S2**).

Patient characteristics by treatment arm are provided in **Table S2**. Over half (53.6%) were male and the median age was 77 years (range, 59-90). Most (78.1%,143/183) had an *FLT3*-ITD mutation without TKD; *FLT3*-ITD AR was balanced between arms. Thirty-one patients had an antecedent hematologic disorder (22 with myelodysplastic syndrome) and 12 had

therapy-related disease. More than half (54.6%, 100/183) had a baseline Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 to 1. Of note, there was an imbalance of baseline ECOG PS scores between GIL+AZA and AZA, with more patients with a worse ECOG PS score of ≥2 in the GIL+AZA arm (48.1%, 50/104) than the AZA arm (35.1%, 20/57) (**Table S2**).

Unless otherwise stated, results are from the total GIL+AZA arm (including both randomized and safety cohorts) and the randomized AZA and GIL monotherapy arms. The median duration (range) of treatment was 169 (2-1787), 114 (4-1029), and 134 (13-534) days in the GIL+AZA (n=103), AZA (n=54), and GIL (n=22) arms. As of the data cutoff on May 31, 2022, only 9 (4.9%) patients remained on study intervention, all of whom were receiving GIL+AZA (**Figure S2**). Among these 9 patients, 6 had *NPM1* co-mutations and 1 patient had received a transplant.

For 8 patients who remained alive at 24 months, the median number of GIL treatment cycles was 26.5 (1022.5 days) and the median number of AZA cycles was 25.5 (1015.0 days). The most common reasons for treatment discontinuation were death in the GIL+AZA arm (28.1%), relapse in the AZA arm (28.1%), and relapse and AEs in the GIL arm (27.3% each). At the final analysis cutoff, median follow-up was 30.1 months for GIL+AZA and not estimable for AZA or GIL.

Following study completion, more than half of patients in the AZA arm (55.6%, 30/54) received subsequent AML therapy (**Table S3**); 50% (15/30) received off-study GIL, constituting 27.8% (15/54) of all AZA-treated patients. Of the AZA-treated patients receiving subsequent AML therapy, 26.7% (8/30) discontinued AZA after 1 study treatment cycle based on investigator's discretion, mostly due to lack of efficacy. By comparison, 24.3% of patients in the GIL+AZA arm (25/103) and 40.9% (9/22) of patients in the GIL arm received subsequent AML therapy. In total, 2.9% of all GIL+AZA (4/103) patients and 9.1% of all GIL (2/22) patients were treated with subsequent off-study GIL. Among patients from the AZA

arm who received subsequent GIL treatment, median OS was 13.77 (95% CI: 8.57, 26.64) months versus 7.46 (95% CI: 3.32, 95.5) months among patients without subsequent GIL treatment. This difference was also seen among patients with a baseline ECOG PS score of 0-1 (AZA with subsequent GIL: 14.88 [95% CI: 4.27, 26.64] months; AZA without subsequent GIL: 8.08 [95% CI: 3.32, 13.37] months).

Survival

Median OS was 9.82 (95% confidence interval [CI]: 8.11, 12.55), 9.23 (95% CI: 4.34, 12.55), and 5.24 (95% CI: 2.46, 15.18) in the GIL+AZA, AZA, and GIL arms, respectively (**Figure 1A**). Differences in median OS between GIL+AZA and AZA were not significant (hazard ratio [HR], 0.829 [95% CI: 0.554, 1.241]; p=0.182). The restricted mean survival time up to 18 months was 10.0 (95% CI: 8.7, 11.4), 9.3 (95% CI: 7.6, 11.0), and 8.7 (95% CI: 5.8, 11.5) months for the GIL+AZA, AZA, and GIL arms, respectively; the difference in restricted mean survival for GIL+AZA versus AZA was 0.7 (95% CI: −1.4, 2.9) months (p=0.511).

We then examined OS rates of each treatment arm at specific time points. The rate of OS, estimated by the Kaplan-Meier method, was similar between GIL+AZA and AZA at 6 and 12 months and was numerically lower in the GIL arm at 6 months (**Table S4**). At 24 months, the OS rate was numerically highest following GIL+AZA (18.8% [95% CI: 11.2%, 27.9%]) as compared with AZA (12.9% [95% CI: 5.2%, 24.3%]) or GIL (4.5% [95% CI: 0.3%, 18.9%]) monotherapy.

In subgroup analyses by mutational profile, differences in median OS were observed in specific subsets. Patients with *FLT3*-ITD AML without a concomitant TKD mutation (11.63 vs 8.87 months; HR, 0.661 [95% CI: 0.440, 0.994]; nominal p=0.047) and AML associated with high *FLT3*-ITD AR (≥0.5) (11.89 vs 7.46 months; HR, 0.515 [95% CI: 0.299, 0.885]; nominal p=0.016) (**Table S5; Figure 2**) achieved significantly longer median OS following GIL+AZA than AZA alone. A trend to longer median OS was also seen following GIL+AZA versus AZA

in patients with ECOG PS scores of 0 to 1 (13.17 vs 9.95 months; nominal p=0.265) and ECOG PS scores of ≥2 (9.00 vs 6.11 months; nominal p=0.246) (**Table S5; Figure S3 and S4**). A trend to shorter median OS was observed following GIL+AZA versus AZA in patients with an *FLT3*-TKD mutation without an ITD mutation (3.02 vs 9.26 months; HR, 2.456 [95% CI: 0.976, 6.179]; nominal p=0.056) (**Table S5**; **Figure 2B**). The inferior outcome for patients with an *FLT3*-TKD mutation without an ITD mutation could be due to an imbalance in baseline ECOG PS score, as 8/19 patients receiving GIL+AZA had a baseline ECOG PS score of ≥2 versus 2/9 patients receiving AZA. Thus, the small sample size and potential imbalance in baseline fitness introduces confounding that precludes firm conclusions.

Since more than half of patients in the AZA arm received subsequent FLT3 inhibitor therapy, which may have impacted their OS, we performed an additional post hoc subgroup analysis based on region of enrollment, to investigate a potential rescue effect of GIL based on the timing of GIL marketing authorization in the R/R setting and availability in different regions. In patients with *FLT3*-ITD mutations alone receiving AZA, the median OS was 10.61 (95% CI: 4.27, 13.37) months in Asia Pacific, 10.22 (95% CI: 3.32, 14.03) months in North America, and 8.08 (95% CI: 2.50, 13.37) months in Europe (**Figure S5**). We also performed an exploratory post hoc analysis using propensity score matching based on ECOG PS score and *FLT3* mutation status in all patients who did not receive subsequent AML therapy. Forty-eight of the 65 patients from the randomized GIL+AZA arm who did not receive subsequent AML therapy were matched to the 24 patients from the AZA arm who did not receive subsequent AML therapy (**Table S6**). In this analysis, patients receiving GIL+AZA had prolonged median OS (9.00 months) versus those receiving AZA monotherapy (3.32 months) (**Figure S6**). This post hoc analysis was not powered for statistical comparison.

A total of 173 EFS events (relapse after CR, treatment failure, or death) occurred (total GIL+AZA: 97/104, 93.3%; AZA: 54/57, 94.7%; randomized GIL: 22/22, 100%). No significant difference was noted in median EFS between GIL+AZA versus AZA (0.03 months for both treatment arms; 95% CI not estimable) (**Figure 1B**). However, sensitivity analyses of EFS

with events based on relapse after composite complete remission (CRc), rather than CR, revealed a significantly longer median EFS for GIL+AZA (median, 4.73 [95% CI: 2.43, 7.56] months) versus AZA (median, 0.03 [95% CI: 0.03, 3.29] months; HR [95% CI], 0.607 [0.415, 0.887]; nominal p=0.008) (**Figure 1C**).

Response Rates

Overall response rates (CRc plus partial remission) were significantly higher in the GIL+AZA arm (73/104, 70.2%) compared with the AZA arm (21/57, 36.8%; treatment difference 32.7% [95% CI: 16.0%, 49.3%]; nominal p<0.001), and numerically similar to those in the GIL arm (16/22, 72.7%) (**Table S7**). Similarly, a significantly higher proportion of patients achieved CRc in the GIL+AZA arm (65/104, 62.5%) versus the AZA arm (16/57, 28.1%; treatment difference 33.9% [95% CI: 17.8%, 50.0%]; nominal p<0.001), while CRc rates in the GIL arm were numerically lower (12/22, 54.5%).

The rates of CR were 26.9% in the GIL+AZA arm, 17.5% in the AZA arm, and 9.1% in the GIL monotherapy arm (**Table S7**). Rates of CR with partial hematological recovery (CRh) were 9.6%, 1.8%, and 22.7% in the GIL+AZA, AZA, and GIL arms, respectively. Median time to CR and median time to best CR or CRh were numerically longer with GIL+AZA than AZA or GIL. While median durations of CR and CRc were numerically longer in the GIL+AZA than AZA or GIL arms (duration of CR not estimable for the GIL arm), the median duration of CRh was numerically longest in the AZA arm.

Among all patients who achieved CR/CRc and had samples available for MRD testing, 17 of 55 (30.9%) patients in the GIL+AZA arm, 4 of 13 (30.8%) patients in the AZA arm, and 4 of 9 (44.4%) patients in the GIL arm achieved MRD negativity at any postbaseline visit over the study period; however, very small patient numbers and inconsistent MRD assessments and available samples precluded comparison and limit interpretability of these results.

Safety

Almost all patients (GIL+AZA, 100%; AZA, 96.3%; GIL, 100%) reported >1 treatment-emergent AE (**Table S8**). When adjusted for treatment exposure, treatment-related AEs (TRAEs) and serious TRAEs were more frequent in the GIL+AZA arm versus AZA, but less frequent than GIL. TRAEs leading to dose reduction or interruption were more frequent following GIL+AZA than AZA or GIL. Deaths were more frequent following AZA than GIL+AZA or GIL (**Table S8**). Among treatment-emergent AEs that occurred in ≥20% of patients in any arm, those that occurred more frequently after GIL+AZA than AZA, when adjusted for treatment exposure, included pyrexia, thrombocytopenia, febrile neutropenia, and nausea (see the full list in **Table S9**). The most common grade ≥3 TRAEs by arm are shown in **Table 1**.

Patient-Reported Outcomes

Overall, PROs were comparable between the GIL+AZA and AZA arms. There were no notable differences for most time points in FACIT-Dys-SF, EQ-5D-5L visual analog scale or utility, and FACT-Leu scores. Mean change from baseline in BFI score was similar between the GIL+AZA and AZA arms at all time points except cycle (C) 1 day (D) 8. There was no clear trend in BFI score change from cycle 1 to the end of treatment in patients receiving GIL+AZA, AZA, or GIL (**Figure S7**).

Pharmacokinetics

In the randomized cohort, mean (SD) GIL plasma trough concentrations (C_{trough}) at C1D15 were comparable between the randomized GIL+AZA (744 ng/mL [433 ng/mL]) and GIL (650 ng/mL [403 ng/mL]) arms.

For all patients with available data, the median GIL C_{trough} for C1D15+C2D1 combined was calculated as 583 ng/mL. Although median OS was numerically shorter in patients with high

(≥583 ng/mL) versus low (<583 ng/mL) GIL C_{trough} values at C1D15+C2D1 (8.11 vs 10.68 months, respectively; HR, 0.771 [95% CI: 0.459, 1.295]; nominal p=0.840), this was not statistically significant (**Figure S8**). Although patients with high GIL C_{trough} values at C1D15+C2D1 had a shorter time to composite discontinuation than patients with low C_{trough} values (median, 1.71 vs 3.25 months, respectively; HR, 0.669 [95% CI: 0.435, 1.027]; nominal p=0.031) (**Figure 3**), there was no apparent correlation between GIL C_{trough} and the development of neutropenia, febrile neutropenia, or thrombocytopenia.

Mutational Profiles

We also performed exploratory analyses of patient subgroups by mutational profiling. Eighty-one patients had *NPM1* mutations at screening (GIL/GIL+AZA, 50.4%; AZA, 41.2%) (**Table S10**). Among these patients, there was a trend to longer median OS following GIL/GIL+AZA versus AZA (11.89 vs 8.57 months; HR, 0.695 [95% CI: 0.400, 1.208]; nominal p=0.197) (**Table 2**). Among 22 patients with *NPM1*/*DMNT3A* co-mutated AML (GIL/GIL+AZA: 17/119 [14.3%]; AZA: 5/51 [9.8%]) (**Table S10**), the median OS was also numerically longer following GIL/GIL+AZA than AZA (15.01 vs 3.29 months; HR, 0.522 [95% CI: 0.182, 1.496]; nominal p=0.226) (**Table 4**). However, these differences were not statistically significant due to small patient numbers and are reported with nominal p-values which should be interpreted with caution.

To better understand mechanisms of innate and acquired resistance, changes in AML mutational profiles were examined prior to and following the protocol therapy. At baseline, all patients had *FLT3* mutations; however, the majority (140/178, 78.7%) had an *FLT3*-ITD mutation without TKD. Twenty-six patients had samples tested for *FLT3* mutation at relapse after study therapy; 3/16 [19%] patients had $FLT3^{mut+}$ AML at relapse after GIL+AZA and 0/5 [0%] patients after GIL compared with 3/5 [60%] patients after AZA only (**Table S11**). Prior to therapy, *RAS/MAPK* pathway mutations were detected in 27 of 119 (22.7%) patients in GIL/GIL+AZA and 3 of 51 (5.9%) AZA-treated patients (**Table S10**). At relapse, *RAS*/*MAPK*

mutations were identified in 12 of 23 (52.2%) patients following GIL/GIL+AZA, of which 9 (39.1%) had new mutations (**Table S12**). In contrast, no *RAS/MAPK* mutant disease was identified at relapse in 5 patients following AZA.

DISCUSSION

We report the final analysis of the phase 3 LACEWING study, which compared the efficacy and safety of GIL+AZA, AZA, or GIL in adults with ND *FLT3*$^{mut+}$ AML ineligible for intensive chemotherapy. Here, the median follow-up for survival with GIL+AZA was 30.06 months versus 12.94 months in the interim analysis. As median OS was already reached at the time of interim analysis, there continues to be no statistically significant difference between the GIL+AZA versus AZA arms with longer follow-up.[14] However, all 9 (4.9%) patients remaining on the study at this later data cutoff were taking GIL+AZA, suggesting a potential long-term benefit of the combination in some patients. This may be reflected in the slight separation between GIL+AZA and AZA Kaplan-Meier OS curves after 12 months, as well as the numerically higher 24-month OS rate following GIL+AZA (18.8%) compared with AZA (12.9%) or GIL (4.5%) (**Figure 1**).

As shown in the prior analysis[14], overall response rates were higher following GIL/GIL+AZA than AZA; despite this, rates of MRD-negative CRc were similar (30.8%-30.9%) between GIL+AZA versus AZA. In addition, similarly high response rates were observed between GIL (72.7%) and GIL+AZA (70.2%) as compared with AZA alone (36.8%), suggesting that potent inhibition of FLT3 signaling alone may be sufficient to significantly cytoreduce proliferating myeloblasts. Among relapsed patients, most patients treated with GIL/GIL+AZA had *FLT3* wild-type relapsed AML, while 60% of patients who received AZA had *FLT3*$^{mut+}$ relapsed AML. This is hypothesized to arise from an outgrowth of non–*FLT3*-ITD AML cells following GIL treatment and the lower AR of patients who relapsed following GIL treatment. This may also suggest that potent suppression of FLT3 by GIL may have led to other compensatory mechanisms of acquired resistance, as opposed to regrowth of *FLT3*$^{mut+}$ AML due to

preexisting mutations following a non-FLT3 inhibitor-containing regimen. Almost 40% (9/23) of patients with *RAS*/*MAPK* mutations following GIL/GIL+AZA treatment had new *RAS*/*MAPK* mutations at relapse, which were not identified at diagnosis, and were consistent with prior known mechanisms of resistance to GIL.[15]

Further exploratory analyses by mutational profile demonstrated subsets of patients who may have benefited from GIL+AZA. Patients with *FLT3*-ITD AML without a TKD mutation, and those with a high *FLT3*-ITD allelic burden (AR ≥0.5), achieved statistically significantly longer median OS following GIL+AZA than AZA (**Figure 2**). These results remain consistent with the interim analysis.[14] Patients with AML characterized by high *FLT3*-ITD AR may respond more favorably to FLT3 inhibitor therapy (ie, GIL+AZA vs AZA) due to a higher degree of *FLT3*-dependent ("*FLT3*-addicted") leukemic disease, which may be inadequately controlled by AZA therapy alone. Potential etiologies of this include *FLT3*-ITD clones early in disease development and/or selective pressure favoring predominance of high numbers of *FLT3*-ITD clones within the overall AML population. In addition, patients with AML with *NPM1* co-mutations, as well as those with triple mutations in *NPM1*, *DNMT3A*, and *FLT3,* achieved numerically longer median OS (11.89 vs 8.57 months and 15.01 vs 3.29 months, respectively) in the GIL/GIL+AZA versus AZA arms. While these results should be interpreted with caution due to an inadequate power, prior data from other trials (ie, ADMIRAL trial of GIL and QuANTUM-First trial of quizartinib)[8,16] have previously demonstrated the clinical benefit of FLT3 inhibitors specifically in this genotype of *NPM1/DMNT3A/FLT3* co-mutated AML.

Here, we report the results of a GIL monotherapy cohort enrolling 22 patients (median age, 78 years) with ND *FLT3*$^{mut+}$ AML. Patients treated with GIL (120 mg daily) achieved a CRc rate of 54.5% (12/22) compared with GIL+AZA (62.5%, 65/104) or AZA (28.1%, 16/57). These responses were similar to the 44% CR+CRi rate observed following GIL monotherapy in 9 patients ≥60 years of age with ND *FLT3*$^{mut+}$ on the BEAT AML study.[17] In that trial, however, many patients received decitabine added to GIL, starting with cycle 3. Here, in the

LACEWING trial, despite this high response rate, patients treated with GIL alone had a shorter OS than those receiving GIL+AZA or AZA therapy. For instance, at 24 months, less than 5% of GIL-treated patients remained alive.

This long-term LACEWING analysis provides information regarding the safety and PK of GIL-based therapy in older patients with ND *FLT3*$^{mut+}$ AML. The safety profile of the GIL+AZA treatment regimen was consistent with the known AE profiles of each individual therapy, with no new safety signals identified. However, compared with AZA, the frequency of TRAEs, serious TRAEs, and TRAEs leading to dose reduction or dose adjustment was higher for patients in the GIL+AZA versus AZA arms.

The PK findings from LACEWING suggest that older patients with ND *FLT3*$^{mut+}$ AML experience higher degrees of GIL exposure than younger individuals. The mean GIL C_{trough} values at C1D15 in these older patients (median age, 77-78 years) treated with GIL+AZA and GIL were 744 ng/ml and 650 ng/mL, respectively. The BEAT clinical study of patients ≥60 years of age with ND AML found similarly elevated C_{trough} steady state values following GIL monotherapy.[17] The levels observed in both the BEAT and LACEWING trials are approximately 1.4- to 2.3-fold higher than reported in the ADMIRAL trial (330 ng/mL at C1D15), which was conducted in younger patients (median age, 62 years) with R/R *FLT3*$^{mut+}$ AML.[14] Similarly, lower GIL C_{trough} values at C1D15 (522 ng/mL) were reported in a phase 1/2 study of younger Asian patients with ND AML, although in that study the C_{trough} value increased to 647 ng/mL by C1D21.[18] In addition to age-related differences in drug disposition, leading to slower drug clearances, other possible causes of increased mean GIL C_{trough} levels in these older patients include altered drug bioavailability[19] or polypharmacy with potentially increased significant drug-drug interactions.[20] While our analyses demonstrated that patients with elevated (≥583 ng/ml) GIL C_{trough} levels had numerically shorter OS, including earlier (composite) discontinuation, no correlation between GIL C_{trough} level and grade of neutropenia or thrombocytopenia in patients was observed. The PK findings therefore remain incompletely understood, likely due to interpatient variability

(including differences in baseline characteristics) and small sample sizes, which limit interpretation and definitive conclusions.

There are several limitations to this study. First, the open-label versus double-blinded study design likely influenced the outcomes by increasing the risk of investigator bias, particularly for those patients randomized to AZA monotherapy. Further, the imbalance in baseline ECOG PS scores between groups may have impacted on survival. The fact that significantly more patients receiving GIL+AZA arm (48.1%) had a worse ECOG PS score (≥2) than in the AZA arm (35.1%) may have contributed to the lack of OS difference between the two arms. The early termination of this study for futility may have prematurely ended this trial prior to longer term determination of any survival difference. Moreover, any analyses of patient subgroups by mutational profiling were limited by small patient numbers and therefore should be interpreted with caution.

Importantly, patient and physician choices to withdraw from the AZA arm may have been affected by the lack of a placebo control arm and the commercial availability of FLT3 inhibitors (including GIL) for the treatment of R/R AML starting in 2018.[9] Over half (55.6%) of patients in the AZA arm received subsequent AML treatment, with 37.0% receiving FLT3 inhibitors (specifically GIL in 27.8%). While this practice was consistent with the on-label use of GIL and treatment algorithms for R/R AML,[6,21] it is likely to have introduced significant confounding that may have impacted OS and EFS differences between arms. Of note, GIL was not obtainable for AML outside of a clinical trial prior to study initiation at many sites but became commercially available for R/R AML during study conduction. To address this limitation, we performed a subgroup analysis based on region of enrollment; results indicate that countries with earlier marketing authorization and commercial availability of GIL in the R/R setting may have led to OS contamination and an improved OS for the AZA arm, highlighting GIL as a rescue/salvage treatment. However, this interpretation is limited by small sample sizes. In addition, a post hoc propensity score matching was performed in patients who had not received subsequent AML therapy. While this demonstrated improved

median OS (9.00 vs 3.32 months) in patients who received GIL+AZA versus AZA, this propensity score matching was conducted based on ECOG PS score and *FLT3* mutation status, and other factors such as myeloid co-mutations were not considered, which possibly impacted survival. Lastly, several exploratory analyses, including outcomes by mutational profiles, CR/CRh duration, MRD status, and mutations at relapse, were assessed post hoc in small numbers of patients and/or inconsistently collected available samples.

This study, together with the VIALE-A trial, laid the groundwork for the development of triplet (FLT3 inhibitor, venetoclax [VEN], and hypomethylating agent) therapy for newly diagnosed *FLT3*$^{mut+}$ AML. A post hoc analysis of the outcomes of *FLT3*$^{mut+}$ patients on the VIALE-A trial demonstrated similar overall response rates (67%) following VEN+AZA as GIL+ AZA (70.2%) versus AZA alone (36%).[22] While the median OS following VEN+AZA in patients with *FLT3*$^{mut+}$ AML was slightly longer (12.5 months) than AZA alone (8.6 months), this appeared to be due largely to the improved outcomes of *FLT3*-TKD AML following VEN+AZA (median OS, 19.2 months). In fact, the median OS of patients with *FLT3*-ITD AML without TKD mutations was slightly longer following GIL+AZA (11.63 months) than VEN+AZA (9.9 months) or AZA (8.87 months). By comparison, the triplet of VEN+GIL+AZA consistently demonstrated superior clinical efficacy to either doublet in *FLT3*$^{mut+}$ AML. Thirty patients treated with this regimen experienced a 96% CR+CRh rate with a median OS of 21.8 months regardless of subsequent allogeneic transplant.[23,24] Outcomes from the phase 1 part of a phase 1/2 multicenter US trial (VICEROY) of the same 3 agents recapitulated these findings with a 90-91% CRc rate and a median OS of 22-23 months.[25]

In summary, this final report of the LACEWING randomized, phase 3 clinical trial showed no significant difference in median OS between GIL+AZA versus AZA as upfront therapy for older patients with ND *FLT3*$^{mut+}$ AML who are ineligible for intensive chemotherapy. However, GIL+AZA combination therapy over ≥2 years may have improved OS compared with AZA alone in some patient subsets, specifically those with an *FLT3*-ITD mutation without a TKD mutation, with a high *FLT3*-ITD AR, and with possible *NPM1/DMT3A/FLT3*

co-mutated disease. Additionally, the high response rate with GIL/GIL+AZA compared with AZA in these patients, along with the unique PK profile of GIL in older adults with ND AML, provides valuable insights for the future development of GIL combinatorial regimens in this difficult-to-treat patient population.

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TABLES

Table 1. Common[a] treatment-related[b] grade ≥3 AEs

Preferred Term[c]	Total GIL+AZA		Randomized GIL		AZA	
	n=103	PY=79.6	n=22	PY=11.3	n=54	PY=21.7
	n (%)	E (E/PY)	n (%)	E (E/PY)	n (%)	E (E/PY)
Neutropenia	25 (24.3)	86 (1.08)	3 (13.6)	15 (1.33)	11 (20.4)	21 (0.97)
Neutrophil count decreased	14 (13.6)	52 (0.65)	2 (9.1)	5 (0.44)	3 (5.6)	3 (0.14)
Febrile neutropenia	25 (24.3)	43 (0.54)	2 (9.1)	4 (0.35)	4 (7.4)	4 (0.18)
Thrombocytopenia	19 (18.4)	34 (0.43)	1 (4.5)	1 (0.09)	7 (13.0)	11 (0.51)
Anemia	19 (18.4)	28 (0.35)	4 (18.2)	4 (0.35)	9 (16.7)	14 (0.65)
White blood cell count decreased	6 (5.8)	18 (0.23)	3 (13.6)	5 (0.44)	2 (3.7)	4 (0.18)
Platelet count decreased	10 (9.7)	15 (0.19)	4 (18.2)	15 (1.33)	8 (14.8)	11 (0.51)

Treatment-related grade ≥3 TRAEs were summarized in the safety analysis set (all patients from the randomization cohort and safety cohort who received ≥1 dose of study drug).

[a]Only treatment-related grade ≥3 TRAEs experienced by ≥10% of patients in either the total GIL+AZA, randomized GIL, or AZA arms are shown.

[b]Treatment-related: TEAEs with possible or probable relationship to study drug as assessed by the investigator, or records where relationship is missing. For GIL+AZA, the combination was considered related if GIL and/or AZA were related.

[c]Preferred Terms were based on MedDRA v23.0.

PY was the total duration of treatment exposure in a year. Sorting order: descending by the frequency (E/PY) of each treatment-related grade ≥3 TEAE in the total GIL+AZA arm; in the case of ties, alphabetical order by Preferred Term was applied.

AE, adverse event; AZA, azacitidine; E, event; GIL, gilteritinib; MedDRA, Medical Dictionary for Regulatory Activities; PY, patient-year; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Table 2. Overall survival by myeloid co-mutation

Co-mutation	GIL/GIL+AZA		AZA		Hazard ratio (95% CI)[b]	P value (2-sided)[c]
	Death events, n/N (%)	Median[a], months	Death events, n/N (%)	Median[a], months		
NPM1	44/60 (73.3)	11.89	18/21 (85.7)	8.57	0.695 (0.400, 1.208)	0.197
NPM1 + *DNMT3a*	12/17 (70.6)	15.01	5/5 (100)	3.29	0.522 (0.182, 1.496)	0.226
RAS/*MAPK*	21/27 (77.8)	8.44	3/3 (100)	13.37	1.399 (0.406, 4.812)	0.595

OS by myeloid co-mutation was calculated using the safety analysis set, which comprised all patients from the randomization cohort and safety cohort who received ≥1 dose of study drug.

[a]Based on Kaplan-Meier estimates.

[b]Hazard ratio for all subjects was based on a stratified Cox proportional hazards model adjusting for age group per IRT, risk groups, and baseline *FLT3* mutation status, with potential of strata pooling. In each subgroup, the hazard ratio (HR) was estimated using an unstratified Cox proportional hazards model. Assuming proportional hazards, a hazard ratio <1 is in favor of arm GIL+AZA.

[c]Nominal p values for comparison between GIL+AZA and AZA; based on Wald test.

AZA, azacitidine; CI, confidence interval; CR, complete remission; CRc, composite complete remission; *DNMT3a*, deoxyribonucleic acid methyltransferase 3 alpha; *FLT3*, FMS-like tyrosine kinase 3; GIL, gilteritinib; IRT, interactive response technology; *MAPK*, mitogen-activated protein kinase; NE, not estimable; *NPM1*, nucleophosmin 1; *RAS*, rat sarcoma.

FIGURE LEGENDS

Figure 1. Kaplan-Meier analysis of A) OS, B) EFS main analysis, and C) EFS sensitivity analysis (total GIL+AZA versus AZA)

OS and EFS analyses by treatment arm were conducted using the full analysis set of patients, which comprised all registered patients from the safety cohort plus all randomized patients from the randomization cohort. EFS was defined as time from randomization to relapse from CR (main analysis) or CRc (sensitivity analysis), treatment failure, or death from any cause (whichever came first). Treatment failure: failing to achieve CRc within six treatment cycles; time-to-treatment failure is set at the date of randomization.

AZA, azacitidine; CI, confidence interval; CR, complete remission; CRc, composite complete remission; EFS, event-free survival; GIL, gilteritinib; HR, hazard ratio; NE, not estimable; OS, overall survival.

Figure 2. Kaplan-Meier analysis of OS for patients with (A) a *FLT3*-ITD mutation without a TKD mutation, (B) a *FLT3*-TKD mutation without an ITD mutation, (C) a high *FLT3*-ITD allelic ratio (≥0.5), and (D) a low *FLT3*-ITD allelic ratio (<0.5) at baseline (total GIL+AZA versus AZA)

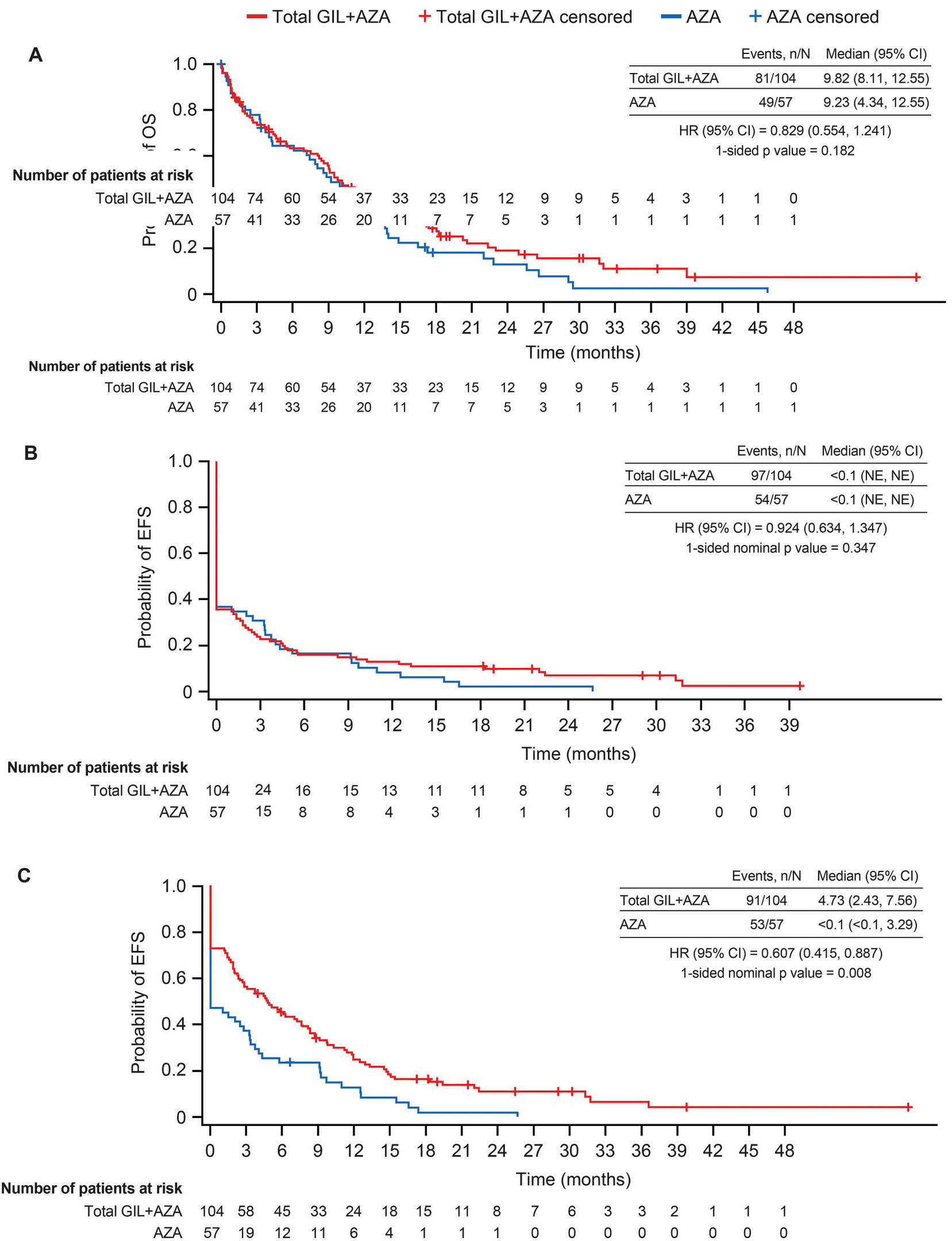
Analyses of OS by baseline FLT3 mutation status and type were conducted using the full analysis set of patients, which comprised all registered patients from the safety cohort plus all randomized patients from the randomization cohort.

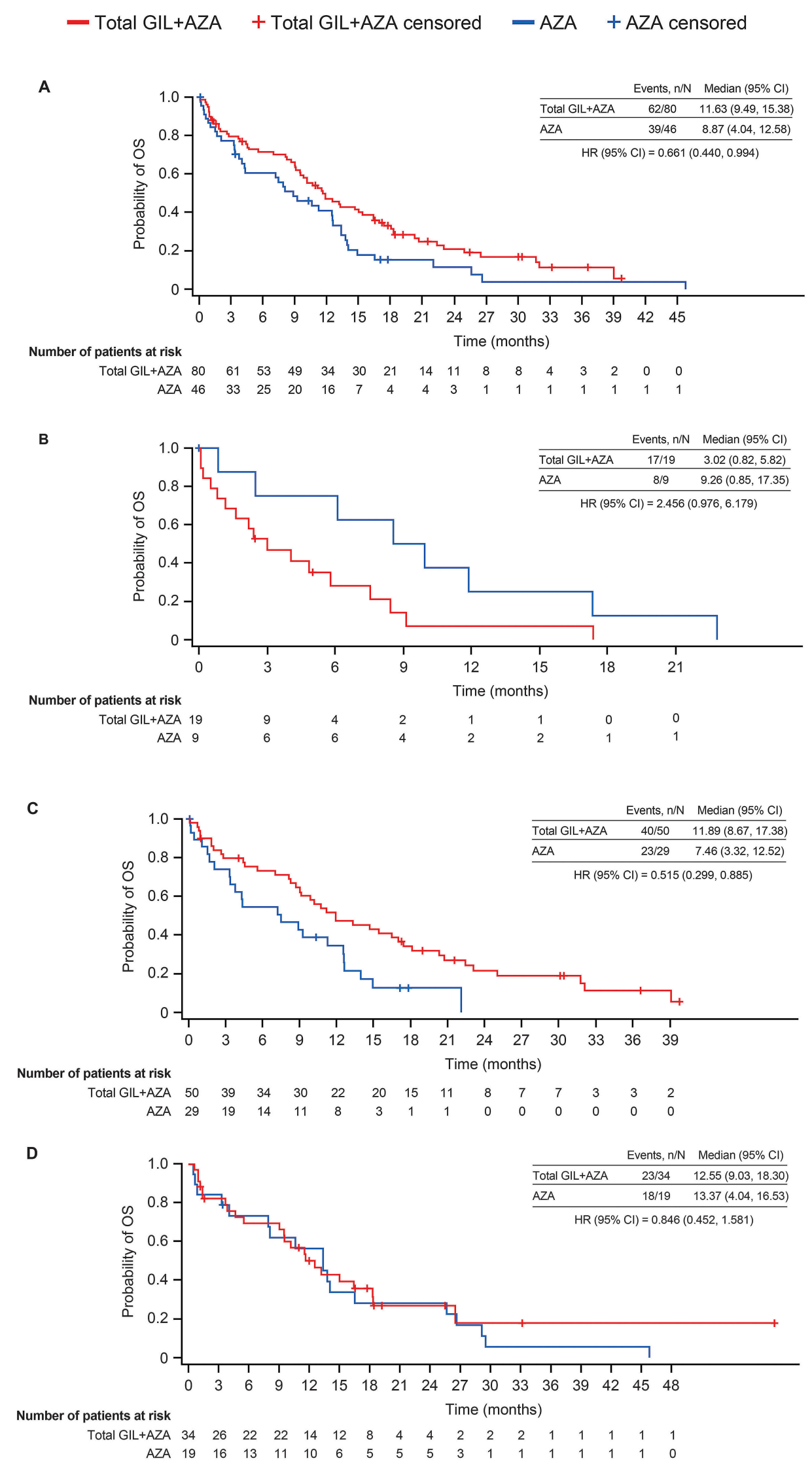
AZA, azacitidine; CI, confidence interval; *FLT3*, FMS-like tyrosine kinase 3; GIL, gilteritinib; HR, hazard ratio; ITD, internal tandem duplication; OS, overall survival.

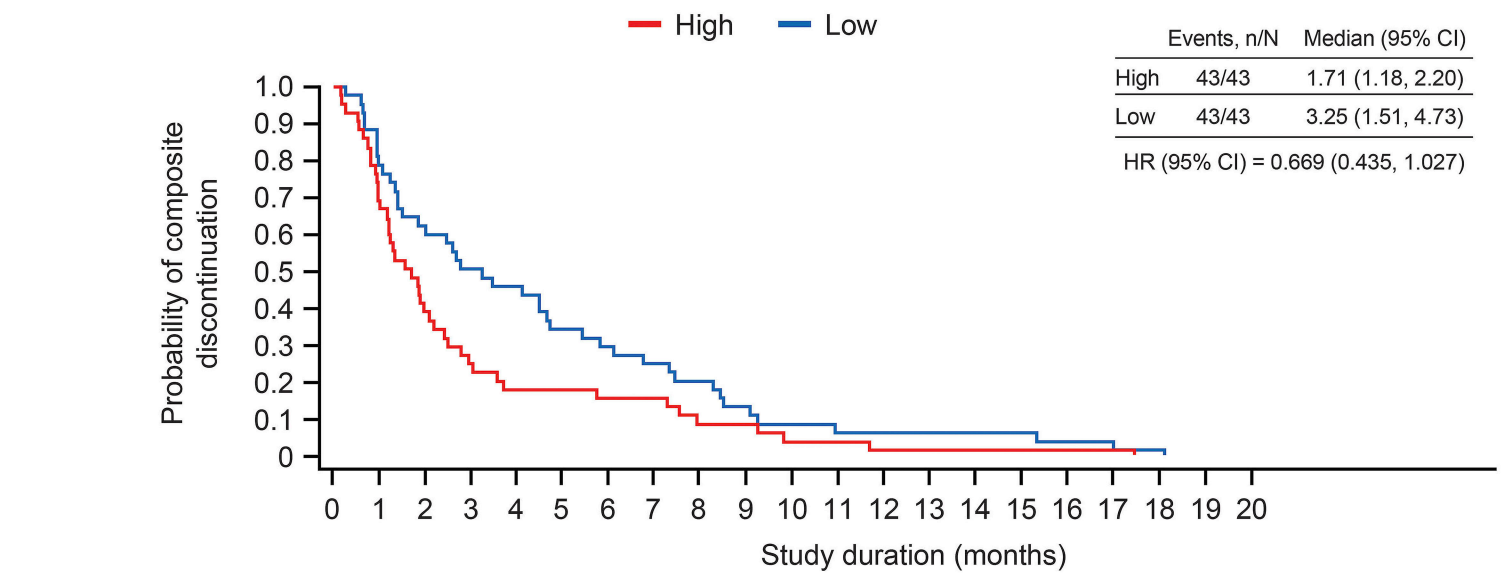
Figure 3. Kaplan-Meier analysis of composite study discontinuation by high versus low gilteritinib C_{trough} values

Analysis of discontinuation was conducted using the pharmacokinetic analysis set, which comprised randomized patients in the SAF who provided at least one sample for the measurement of drug concentrations and for whom both the date and time of dosing and of PK sampling were known. Composite discontinuation: treatment discontinuation, treatment pause of ≥7 days, or decrease in treatment dose. High C_{trough} was defined as ≥583 ng/mL, which was the median C_{trough} on cycle 1 day 15 and cycle 2 day 1 combined, for all patients with available data; low C_{trough} was defined as <583 ng/mL.

CI, confidence interval; C_{trough}, plasma trough concentration.


Total GIL+AZA
Total GIL+AZA censored
AZA
AZA censored
A
Events, n/N
Median (95% CI)
Total GIL+AZA 81/104 9.82 (8.11, 12.55)
AZA 49/57 9.23 (4.34, 12.55)
HR (95% CI) = 0.829 (0.554, 1.241)
1-sided p value = 0.182
Number of patients at risk
Total GIL+AZA 104 74 60 54 37 33 23 15 12 9 9 5 4 3 1 1 0
AZA 57 41 33 26 20 11 7 7 5 3 1 1 1 1 1 1 1
Time (months)
B
Probability of EFS
Events, n/N
Median (95% CI)
Total GIL+AZA 97/104 <0.1 (NE, NE)
AZA 54/57 <0.1 (NE, NE)
HR (95% CI) = 0.924 (0.634, 1.347)
1-sided nominal p value = 0.347
Number of patients at risk
Total GIL+AZA 104 24 16 15 13 11 11 8 5 5 4 1 1 1
AZA 57 15 8 8 4 3 1 1 1 0 0 0 0 0
Time (months)
C
Probability of EFS
Events, n/N
Median (95% CI)
Total GIL+AZA 91/104 4.73 (2.43, 7.56)
AZA 53/57 <0.1 (<0.1, 3.29)
HR (95% CI) = 0.607 (0.415, 0.887)
1-sided nominal p value = 0.008
Number of patients at risk
Total GIL+AZA 104 58 45 33 24 18 15 11 8 7 6 3 3 2 1 1 1
AZA 57 19 12 11 6 4 1 1 1 0 0 0 0 0 0 0 0
Time (months)


Total GIL+AZA
Total GIL+AZA censored
AZA
AZA censored
A
Probability of OS
Time (months)
Events, n/N
Median (95% CI)
Total GIL+AZA 62/80 11.63 (9.49, 15.38)
AZA 39/46 8.87 (4.04, 12.58)
HR (95% CI) = 0.661 (0.440, 0.994)
Number of patients at risk
Total GIL+AZA 80 61 53 49 34 30 21 14 11 8 8 4 3 2 0 0
AZA 46 33 25 20 16 7 4 4 3 1 1 1 1 1 1 1
B
Probability of OS
Time (months)
Events, n/N
Median (95% CI)
Total GIL+AZA 17/19 3.02 (0.82, 5.82)
AZA 8/9 9.26 (0.85, 17.35)
HR (95% CI) = 2.456 (0.976, 6.179)
Number of patients at risk
Total GIL+AZA 19 9 4 2 1 1 0 0
AZA 9 6 6 4 2 2 1 1
C
Probability of OS
Time (months)
Events, n/N
Median (95% CI)
Total GIL+AZA 40/50 11.89 (8.67, 17.38)
AZA 23/29 7.46 (3.32, 12.52)
HR (95% CI) = 0.515 (0.299, 0.885)
Number of patients at risk
Total GIL+AZA 50 39 34 30 22 20 15 11 8 7 7 3 3 2
AZA 29 19 14 11 8 3 1 1 0 0 0 0 0 0
D
Probability of OS
Time (months)
Events, n/N
Median (95% CI)
Total GIL+AZA 23/34 12.55 (9.03, 18.30)
AZA 18/19 13.37 (4.04, 16.53)
HR (95% CI) = 0.846 (0.452, 1.581)
Number of patients at risk
Total GIL+AZA 34 26 22 22 14 12 8 4 4 2 2 2 1 1 1 1 1
AZA 19 16 13 11 10 6 5 5 5 3 1 1 1 1 1 1 0



Number of patients at risk

High	43	30	17	11	8	8	7	7	4	4	2	2	1	1	1	1	1	1	0	0	0
Low	43	34	27	22	20	15	13	11	9	6	4	3	3	3	3	3	2	2	1	0	0

SUPPLEMENTARY DATA

Article Title: Gilteritinib plus azacitidine in patients with newly diagnosed *FLT3* mutation-positive acute myeloid leukemia who were ineligible for intensive chemotherapy: final results of the phase 3 LACEWING study

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Running title (49/50 characters): Gilteritinib + azacitidine in patients with *FLT3*$^{mut+}$ AML

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SUPPLEMENTARY METHODS

Intensive induction chemotherapy ineligibility criteria

- ≥65 years of age and ineligible for intensive induction chemotherapy per investigator's discretion
- ≥18 to 64 years of age and with any of the following comorbidities:
    - Congestive heart failure (New York Heart Association class ≤3) or ejection fraction ≤50%
    - Creatinine >2 mg/dL (177 µmol/L), dialysis, or prior renal transplant
    - Eastern Cooperative Oncology Group performance status ≥2
    - Prior or current malignancy that did not require concurrent treatment
    - Received a cumulative anthracycline dose above 400 mg/m^2 of doxorubicin (or cumulative maximum dose of another anthracycline)
    - Known pulmonary disease with decreased diffusion capacity of lung for carbon monoxide (>50%) and/or requiring oxygen ≤2 L/min
    - Any other comorbidity that the physician judged to be incompatible with intensive chemotherapy, with review and approval by the Medical Monitor during screening and before randomization.

Exclusion criteria

Exclusion criteria included acute promyelocytic leukemia, *BCR*:*ABL*-positive leukemia, clinically active central nervous system leukemia, or major surgery/radiation therapy ≤4 weeks before first study dose.

Patient assessments

Patients had an end-of-treatment visit within 7 days after the last dose of study treatment, followed by a 30-day follow-up for safety data and survival status. Subsequent acute myeloid leukemia (AML) therapies received after the last dose of study treatment, remission status, and survival status were collected for patients who did not withdraw consent during the long-term follow-up (up to 3 years).

Patient samples were collected during the study for additional analyses. Pre-dose plasma samples for pharmacokinetic (PK) analysis were collected on days 1, 8, and 15 of cycle 1, and day 1 of subsequent cycles. Individual mean plasma trough concentrations (C_{trough}) were calculated as the mean C_{trough} of cycle 1 day 15 (C1D15) and cycle 2 day 1 (C2D1). Gilteritinib (GIL) C_{trough} groups were defined based on the median GIL C_{trough} value calculated for all patients with available data: an individual's mean C_{trough} values were categorized as high if they were greater than or equal to the median GIL C_{trough} value; otherwise, they were categorized as low.

Measurable residual disease (MRD) was assessed as the ratio of FMS-like tyrosine kinase 3-mutated (*FLT3*) internal tandem duplication (ITD) DNA sequencing reads to total *FLT3* sequencing reads, using next-generation sequencing, and was defined as negative if the sum of each individual *FLT3*-ITD mutation ratio was $\leq 10^{-4}$ at any post-baseline timepoint. MRD testing was conducted at a central laboratory. The *FLT3*-ITD MRD limit of detection was 5×10^{-5} and the limit of blank was 1×10^{-6}. Results reported represent the best MRD response at any time. No MRD measurements by flow cytometry were performed.

Analysis of myeloid gene co-mutations was performed by next-generation sequencing of blood and bone marrow samples;[8] patients were categorized as having a *RAS*/*MAPK* pathway mutation if they had a mutation detected in any of the following: *BRAF*, *CBL*, *KRAS*, *NRAS*, or *PTPN11*.

Patient-reported outcomes (PRO) were assessed using the Brief Fatigue Inventory (BFI), Functional Assessment of Chronic Illness Therapy-Dyspnea Short Form (FACIT-Dys-SF), Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu), scores for dizziness and mouth sores, and the EuroQol Group 5 Dimension 5 Level (EQ-5D-5L).

Statistical Analyses

The planned sample size was approximately 250 patients. The protocol-specified boundary for study termination due to futility was p≥0.724 for an unfavorable outcome in overall survival (OS) for GIL + azacitidine (AZA) versus AZA monotherapy. An interim analysis conducted after 70 deaths had occurred (data cutoff, August 26, 2020) calculated the median OS to be 9.82 and 8.87 months for the randomized GIL+AZA and AZA arms, respectively (hazard ratio [HR] 0.916 [95% confidence interval (CI): 0.529, 1.585]; p=0.753). Patient enrollment was therefore stopped on December 17, 2020; 183 participants had been enrolled up to this date. This final analysis presents data through the cutoff date of May 31, 2022.

The safety cohort included patients who registered to receive GIL+AZA. The randomized cohort comprised all patients randomized to GIL+AZA, AZA, or GIL. Demographics and baseline characteristics, efficacy endpoints, and patient-reported outcomes (PROs) were summarized and analyzed based on the randomization arms using the full analysis set, which comprised all registered patients from the safety cohort plus all randomized patients from the randomization cohort. Analyses of subsequent AML therapy, evaluation of mutation status at baseline/screening and relapse, and all safety and tolerability variables were summarized and analyzed based on treatment received at the first dose, using the safety analysis set (all patients from the randomization cohort and safety cohort who received ≥1 dose of study drug). The PK analysis set comprised randomized patients in the safety analysis set who provided ≥1 sample for the measurement of drug concentrations and for whom both the date and time of dosing and of PK sampling were known.

OS was analyzed for all patients in the full analysis set, by baseline subgroups of interest (age, sex, race, baseline Eastern Cooperative Oncology Group Performance Status [ECOG PS], risk group, baseline *FLT3* mutation type, baseline *FLT3* mutation status [high vs low allelic ratio), and by high versus low GIL C_{trough} value. Time-to-event endpoints (OS, event-free survival, and remission duration) were summarized using Kaplan-Meier estimates, and comparisons were based on stratified log-rank tests. Median follow-up times with 95% CIs were obtained using the reverse Kaplan-Meier method.

A *post hoc* analysis of OS for patients who did not receive subsequent AML therapy was conducted using propensity score matching to reduce potential bias due to differences in ECOG PS and *FLT3* mutation status at baseline. OS was then compared between the matched cohorts using Kaplan-Meier estimates.

A sensitivity analysis of OS was performed, using a test for equality of two survival functions based on weighted differences of Kaplan-Meier curves with estimation of difference of restricted mean survival time and its 95% CI. This analysis prespecified a cutoff time of 18 months as a timepoint when at least 10% of the randomized patients would still be in follow-up for survival in both arms, to ensure a robust estimate of the mean survival time.

Sensitivity analysis of event-free survival was performed with events based on relapse after composite CR rather than complete remission.

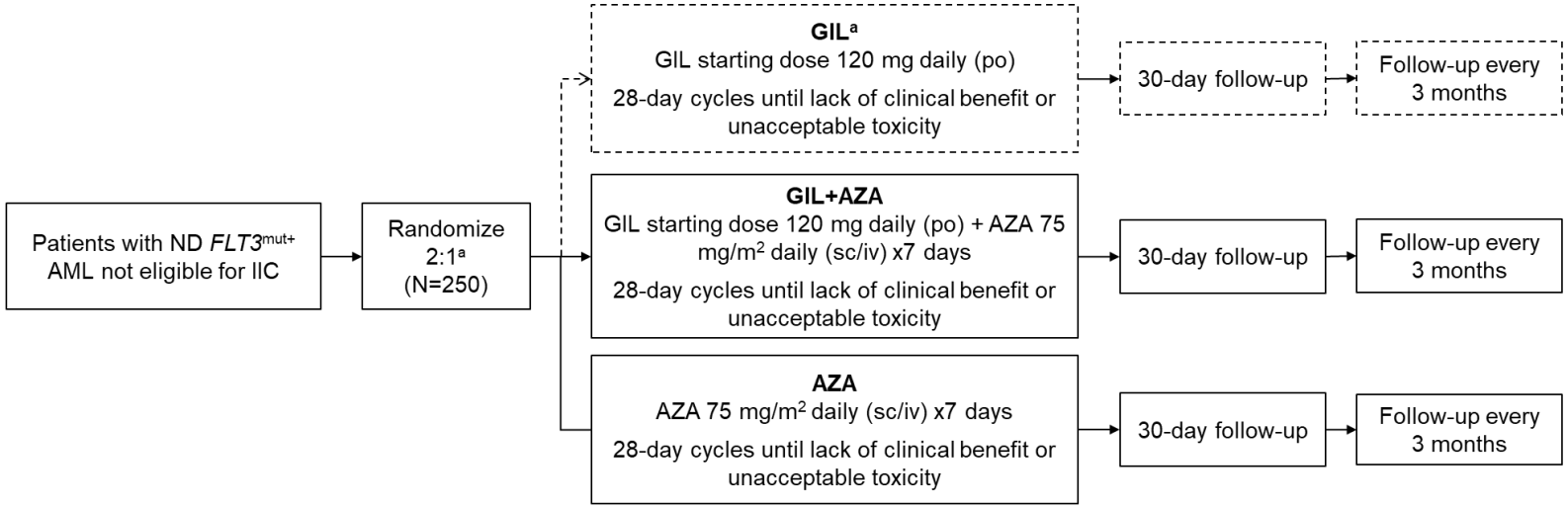
Response was summarized with frequency counts and percentages, with exact 95% CIs based on binomial distribution, and comparisons based on the Cochran-Mantel-Haenszel test.

Composite discontinuation (defined as treatment discontinuation, pause ≥7 days, or decrease in dose) was analyzed by high versus low GIL C_{trough} value using the Kaplan-Meier method.

Statistical comparisons were conducted for total GIL+AZA (including patients from both randomized and safety cohorts) versus AZA, while the randomized GIL arm was summarized descriptively. As the study was powered for OS in the total GIL+AZA versus AZA arm, p values reported for other endpoints and subgroups are nominal.

SUPPLEMENTARY FIGURES

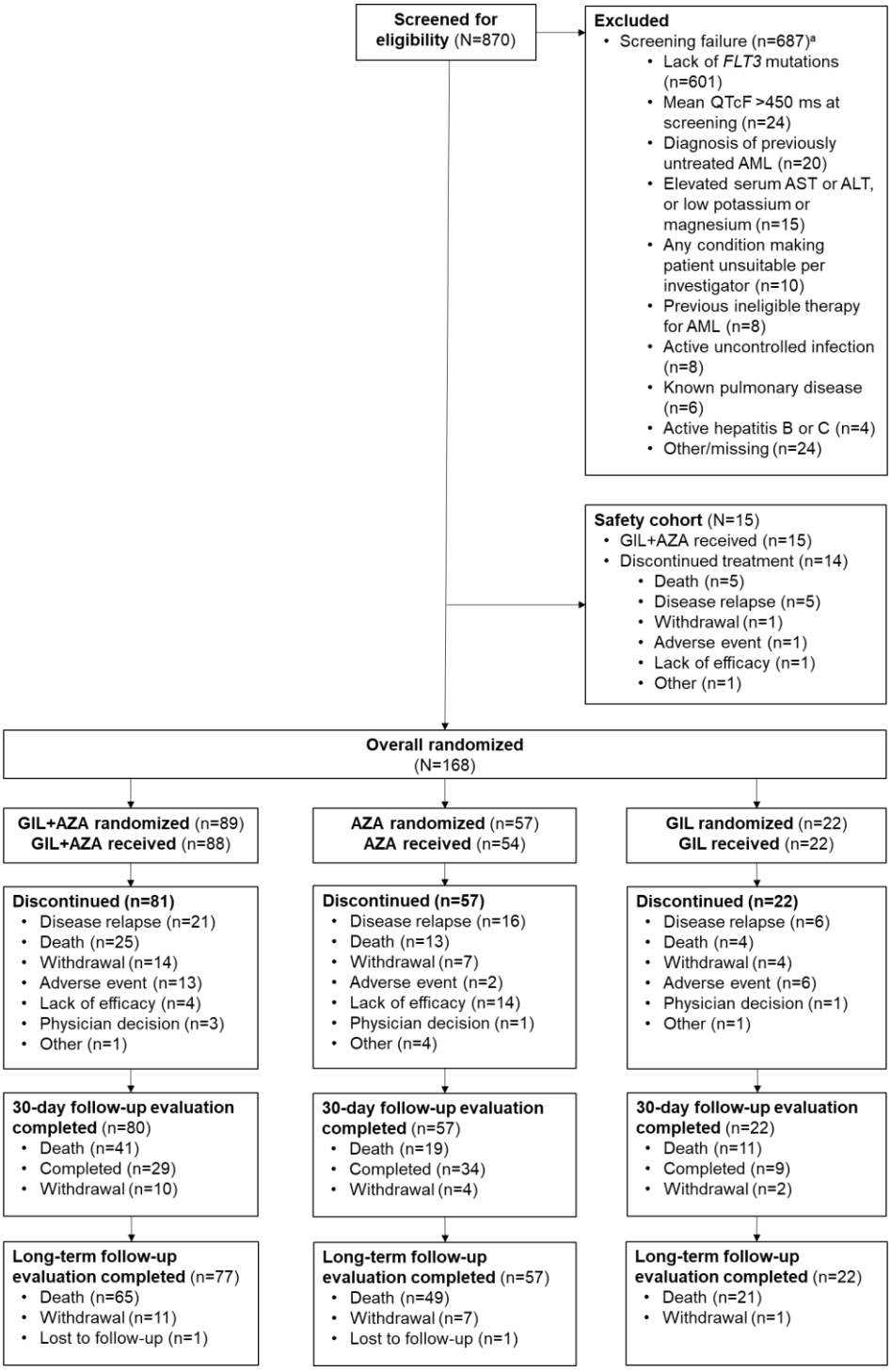
Figure S1. Study design



[a]In the initial study design, patients were randomized 1:1:1 to GIL+AZA, GIL monotherapy, or AZA monotherapy. The GIL monotherapy arm was discontinued on September 05, 2018 (approximately 12 months after initiation of the randomized cohort); patients enrolled in this arm continued GIL monotherapy until unacceptable toxicity, loss of clinical benefit, or another treatment discontinuation criterion occurred. In a revised study design, patients were randomized 2:1 to either GIL+AZA or AZA monotherapy.

AML, acute myeloid leukemia; AZA, azacitidine; FLT3, FMS-like tyrosine kinase 3; GIL, gilteritinib; IIC, intensive induction chemotherapy; IV, intravenous; mut+, mutation positive; ND, newly diagnosed; PO, oral administration; SC, subcutaneous.

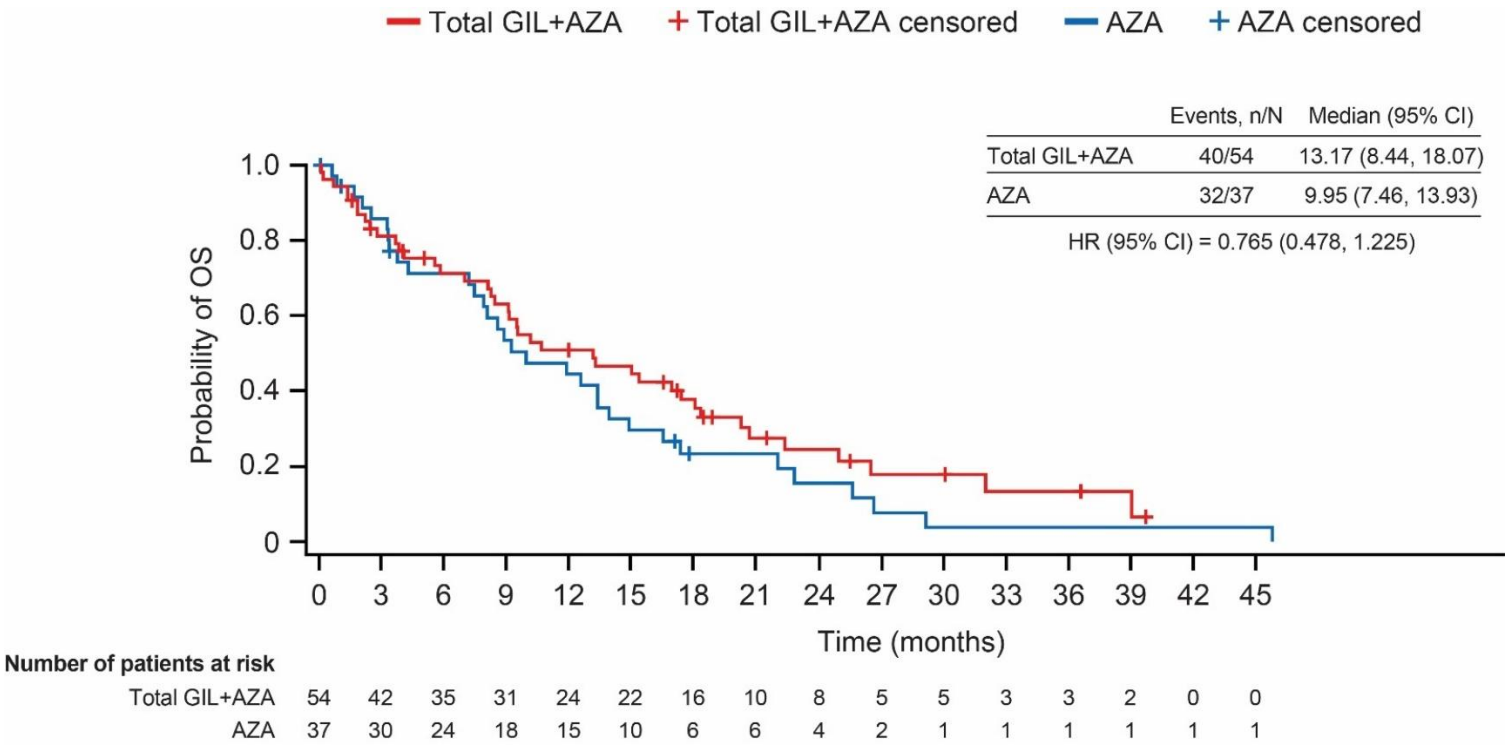
Figure S2. Patient disposition



[a]Patients may be counted more than once in the individual reasons for screening failure if more than one reason occurred.

AML, acute myeloid leukemia; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AZA, azacitidine; *FLT3*, FMS-like tyrosine kinase 3; GIL, gilteritinib.

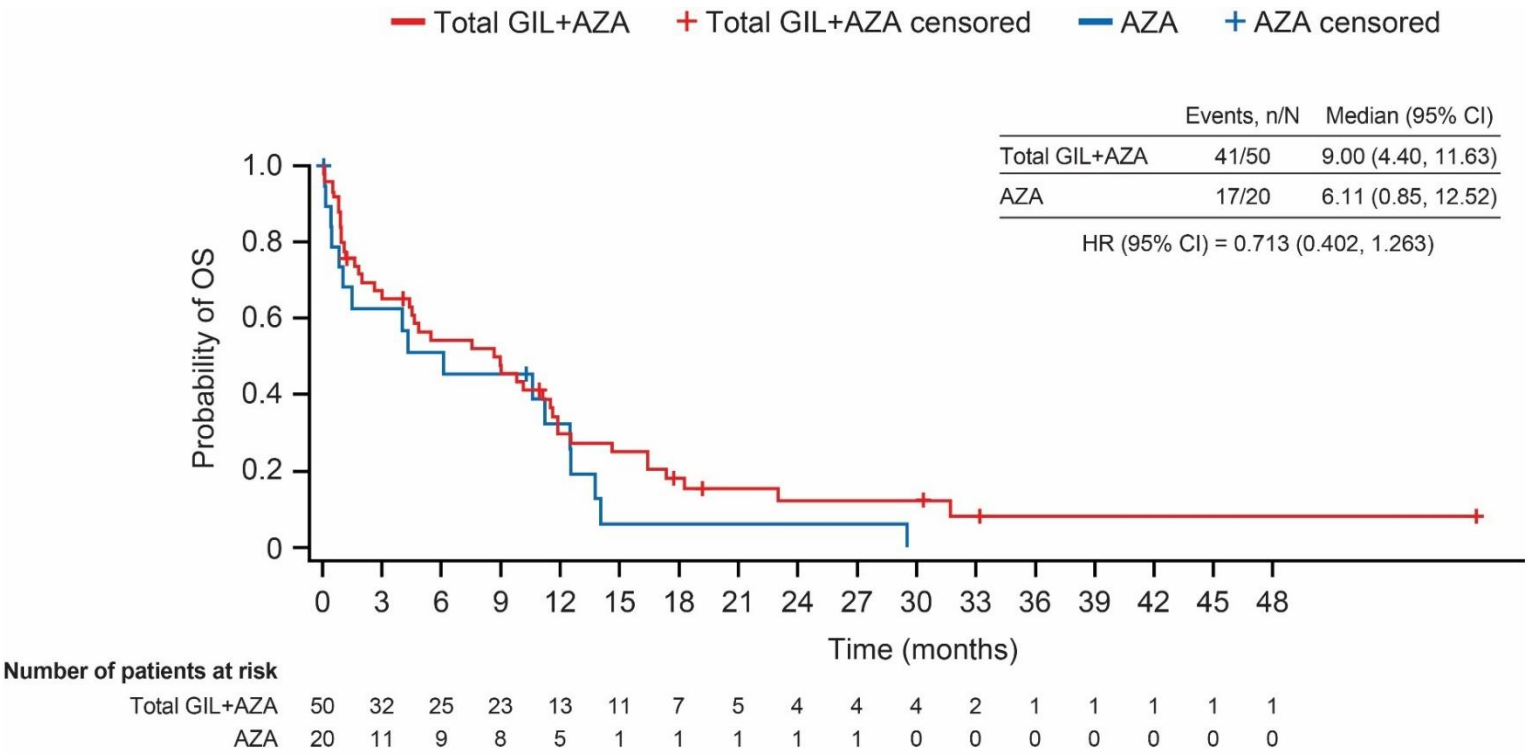
Figure S3. Kaplan-Meier analysis of OS for patients with ECOG PS 0–1 at baseline (total GIL+AZA versus AZA)



Analysis of OS by baseline ECOG was conducted using the full analysis set of patients, which comprised all registered patients from the safety cohort plus all randomized patients from the randomization cohort.

AZA, azacitidine; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; GIL, gilteritinib; HR, hazard ratio; OS, overall survival; PS, performance status.

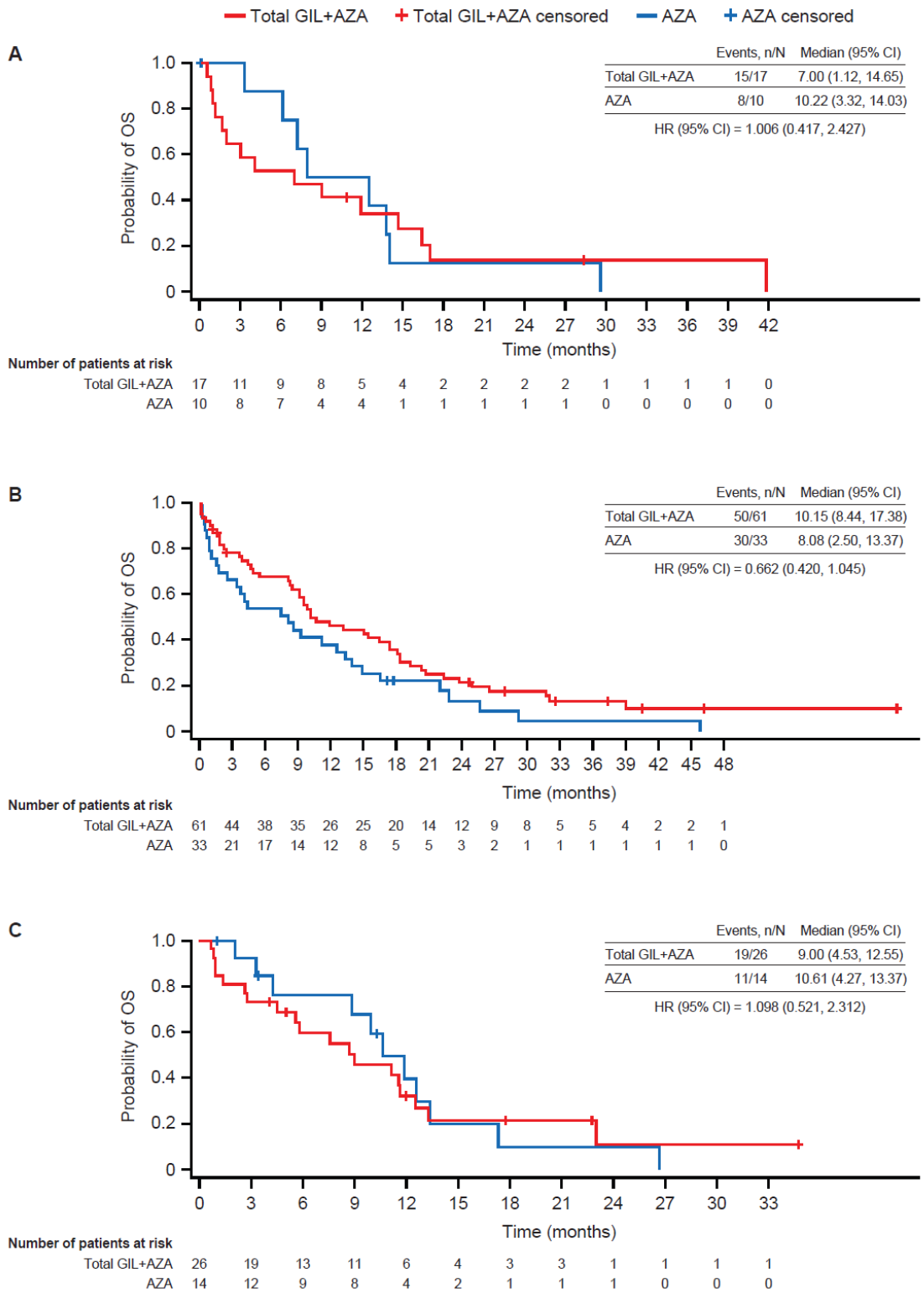
Figure S4. Kaplan-Meier analysis of OS for patients with ECOG PS ≥2 at baseline (total GIL+AZA versus AZA)



Analysis of OS by baseline ECOG was conducted using the full analysis set of patients, which comprised all registered patients from the safety cohort plus all randomized patients from the randomization cohort.

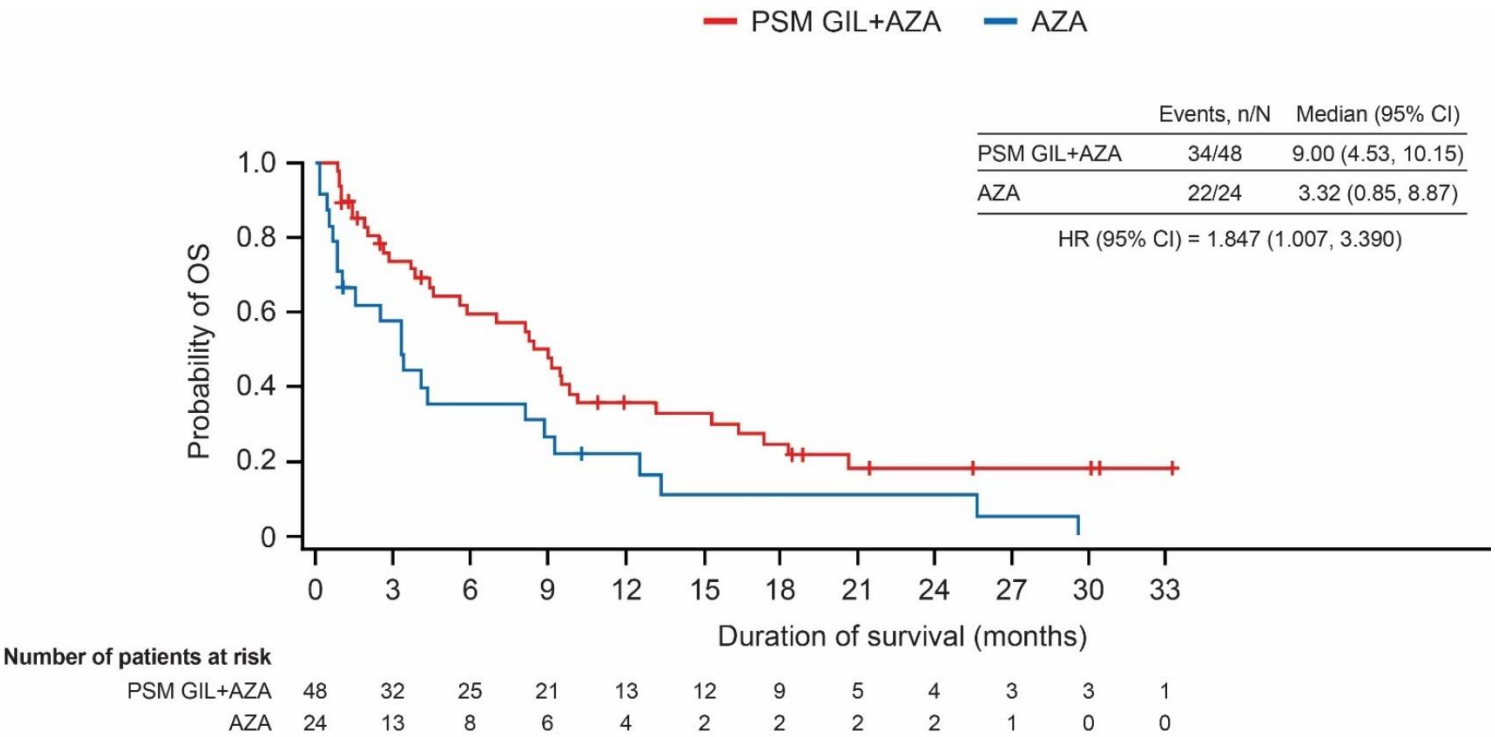
AZA, azacitidine; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; GIL, gilteritinib; HR, hazard ratio; OS, overall survival; PS, performance status.

Figure S5. Kaplan-Meier analysis of OS for patients with *FLT3*-ITD mutations enrolled in (A) Asia Pacific, (B) North America, and (C) Europe



AZA, azacitidine; CI, confidence interval; *FLT3*, FMS-like tyrosine kinase 3; GIL, gilteritinib; HR, hazard ratio; ITD, internal tandem duplication; OS, overall survival.

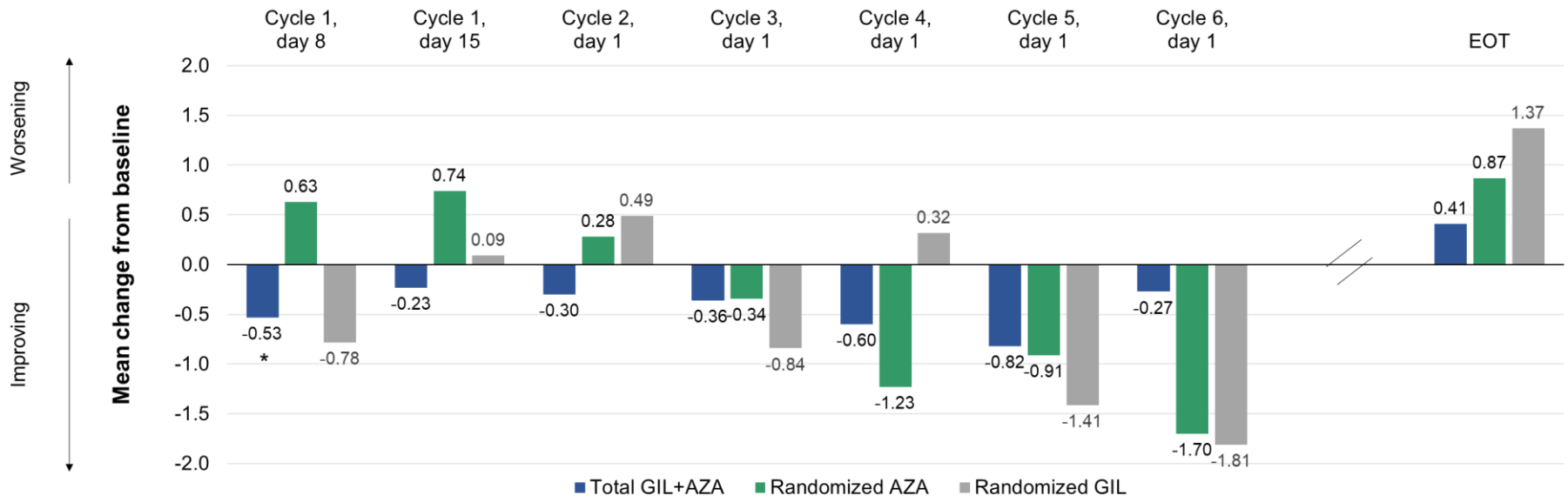
Figure S6. Kaplan-Meier analysis of OS for patients without subsequent AML therapy: propensity score matched patients randomized to GIL+AZA versus AZA



Analysis of OS after propensity score matching was conducted using the full analysis set of patients, which comprised all registered patients from the safety cohort plus all randomized patients from the randomization cohort.

AML, acute myeloid leukemia; AZA, azacitidine; GIL, gilteritinib; OS, overall survival; PSM, propensity score matched.

Figure S7. Change from baseline in BFI score

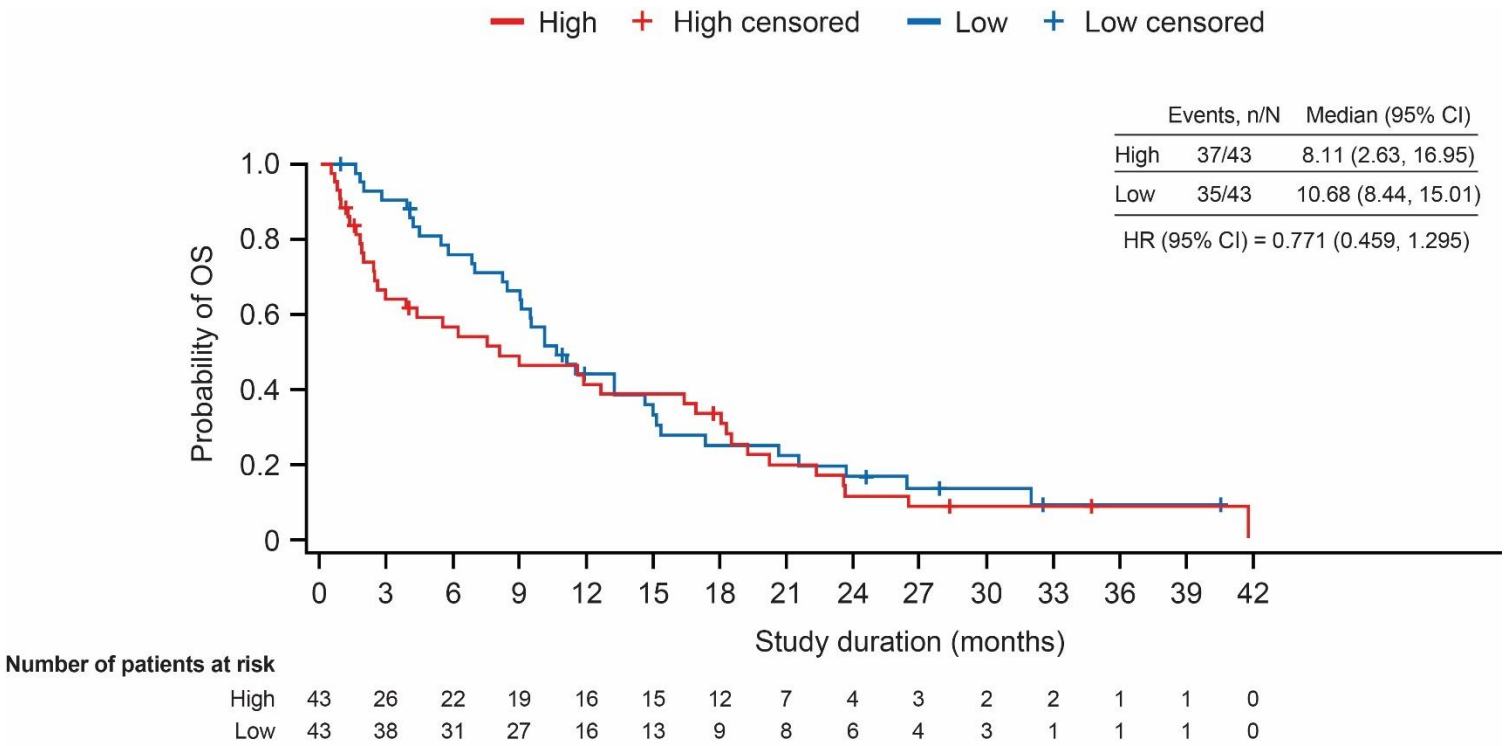


BFI scores were calculated using the full analysis set, which comprised all registered patients from the safety cohort plus all randomized patients from the randomization cohort.

*Nominal $p<0.05$ for total GIL+AZA versus the AZA arm, using analysis of covariance including treatment and age group per interactive response technology as fixed factors, and baseline score as a covariate.

AZA, azacitidine; BFI, Brief Fatigue Inventory; EOT, end of treatment; GIL, gilteritinib.

Figure S8. Kaplan-Meier analysis of OS by high versus low gilteritinib C_{trough} value



Analysis of OS by C_{trough} was conducted in the pharmacokinetic analysis set, which comprised randomized patients in the SAF who provided at least one sample for the measurement of drug concentrations and for whom both the date and time of dosing and of PK sampling were known.

High C_{trough} was defined as ≥583 ng/mL, which was the median C_{trough} on cycle 1 day 15 and cycle 2 day 1 combined, for all patients with available data; low C_{trough} was defined as <583 ng/mL.

CI, confidence interval; C_{trough}, plasma trough concentration; HR, hazard ratio; OS, overall survival.

SUPPLEMENTARY TABLES

Table S1. Definitions of response parameters

Response parameter	Definition
Complete remission (CR)	• Presence of regenerating hematopoietic cells in the bone marrow • A morphologic leukemia-free state • ANC ≥1 × 10^9/L and platelet count ≥100 × 10^9/L • Normal bone marrow differential with <5% blasts • Peripheral blood blasts ≤2% • RBC and platelet transfusion independence (≥1 week without RBC transfusion and platelet transfusion) • No evidence of extramedullary leukemia • No evidence of Auer rods
Complete remission with partial hematologic recovery (CRh)	• Bone marrow blasts <5%, • Partial hematologic recovery: ANC ≥0.5 × 10^9/L and platelets ≥ 50 × 10^9/L • Peripheral blood blasts ≤2% • No evidence of extramedullary leukemia • Cannot be classified as CR
Complete remission with incomplete platelet recovery (CRp)	Achievement of all CR criteria except for incomplete platelet recovery (<100 × 10^9/L)
Complete remission with incomplete hematologic recovery (CRi)	Achievement of all CR criteria except for incomplete hematological recovery: residual neutropenia (ANC <1 × 10^9/L), with or without complete platelet recovery. RBC and platelet transfusion independence is not required
Composite complete remission (CRc)	CR, CRp + CRi

Partial remission (PR)	Response is classified as PR if: • Bone marrow blasts ≥5–25%, with a decrease of ≥50% from baseline • Peripheral blood blast count ≤2% • No evidence of extramedullary leukemia Response may also be considered PR if bone marrow myeloblasts <5% but Auer rods are present
Overall response	CRc + PR
Best response	The best measured response from all post-baseline visits, in the order of CR, CRp, CRi, or treatment failure
Relapse	Relapse after CR, CRp, or CRi was defined as a reappearance of leukemic blasts (>2%) in peripheral blood or ≥5% myeloblasts in the bone marrow aspirate not attributable to any other cause, or reappearance/new appearance of extramedullary leukemia Relapse after PR was defined as reappearance of significant numbers of peripheral blasts (>2%) and increase in percentage of blasts in the bone marrow aspirate to >25% not attributable to any other cause, or reappearance/new appearance of extramedullary leukemia
Treatment failure	Failure to achieve CR within six treatment cycles

ANC, absolute neutrophil count; 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; PR, partial remission; RBC, red blood cell.

Table S2. Patient demographics and disease characteristics

	Total GIL+AZA (n=104)	Randomized GIL (n=22)	AZA (n=57)	Total (N=183)
Sex, n (%)				
Male	56 (53.8)	12 (54.5)	30 (52.6)	98 (53.6)
Female	48 (46.2)	10 (45.5)	27 (47.4)	85 (46.4)
Ethnicity, n (%)				
Hispanic or Latino	2 (1.9)	1 (4.5)	4 (7.0)	7 (3.8)
Not Hispanic or Latino	89 (85.6)	18 (81.8)	46 (80.7)	153 (83.6)
Unknown	13 (12.5)	3 (13.6)	7 (12.3)	23 (12.6)
Race, n (%)				
White	64 (61.5)	9 (40.9)	33 (57.9)	106 (57.9)
Asian	28 (26.9)	10 (45.5)	15 (26.3)	53 (29.0)
Other	0	1 (4.5)	1 (1.8)	2 (1.1)
Unknown	12 (11.5)	2 (9.1)	8 (14.0)	22 (12.0)
Age (years)				
Median (min, max)	77.5 (59, 90)	78.0 (71, 88)	76.0 (61, 88)	77.0 (59, 90)
Age group per IRT (years), n (%)				
<75	33 (31.7)	4 (18.2)	15 (26.3)	52 (28.4)
≥75	71 (68.3)	18 (81.8)	42 (73.7)	131 (71.6)
Region, n (%)				
North America	17 (16.3)	4 (18.2)	10 (17.5)	31 (16.9)
Europe	61 (58.7)	8 (36.4)	33 (57.9)	102 (55.7)
Asia/Pacific	26 (25.0)	10 (45.5)	14 (24.6)	50 (27.3)
Baseline ECOG PS, n (%)				
0–1	54 (51.9)	9 (40.9)	37 (64.9)	100 (54.6)

	Total GIL+AZA (n=104)	Randomized GIL (n=22)	AZA (n=57)	Total (N=183)
≥2	50 (48.1)	13 (59.1)	20 (35.1)	83 (45.4)
Weight (kg)				
Median (min, max)	68.0 (42.1, 146.8)	63.8 (38.9, 102.0)	64.1 (37.4, 128.4)	66.9 (37.4, 146.8)
Height (cm)				
n	104	21	57	182
Median (min, max)	165.2 (144.0, 184.1)	165.0 (150.3, 190.0)	162.0 (139.1, 186.0)	165.0 (139.1, 190.0)
BMI (kg/m^2)				
n	104	21	57	182
Median (min, max)	25.2 (17.2, 43.3)	22.1 (14.8, 39.8)	25.3 (17.3, 45.0)	24.9 (14.8, 45.0)
BSA (m^2)				
n	103	21	54	178
Median (min, max)	1.8 (1.3, 2.7)	1.7 (1.3, 2.2)	1.7 (1.2, 2.5)	1.8 (1.2, 2.7)
Baseline *FLT3* mutation type, n (%)				
ITD without TKD	80 (76.9)	17 (77.3)	46 (80.7)	143 (78.1)
TKD (D835/I836) without ITD	19 (18.3)	2 (9.1)	9 (15.8)	30 (16.4)
ITD with TKD (D835/I836)	4 (3.8)	3 (13.6)	2 (3.5)	9 (4.9)
Others (unknown/missing/negative)	1 (1.0)	0	0	1 (0.5)
Baseline *FLT3* mutation status, n (%)[a]				
ITD LAR (<0.5)	34 (32.7)	8 (36.4)	19 (33.3)	61 (33.3)
ITD HAR (≥0.5)	50 (48.1)	12 (54.5)	29 (50.9)	91 (49.7)
TKD	19 (18.3)	2 (9.1)	9 (15.8)	30 (16.4)
Missing	1 (1.0)	0	0	1 (0.5)
Cytogenetic risk status, n (%)[b]				
Favorable	2 (1.9)	0	0	2 (1.1)

	Total GIL+AZA (n=104)	Randomized GIL (n=22)	AZA (n=57)	Total (N=183)
Intermediate	74 (71.2)	17 (77.3)	40 (70.2)	131 (71.6)
Unfavorable	10 (9.6)	0	6 (10.5)	16 (8.7)
Others (unknown, missing)	18 (17.3)	5 (22.7)	11 (19.3)	34 (18.6)
WBC count category, n (%)[c]				
Low (<10 × 10^3/μL)	61 (58.7)	12 (54.5)	31 (54.4)	104 (56.8)
Intermediate (≥10 × 10^3/μL to <50 × 10^3/μL)	37 (35.6)	9 (40.9)	20 (35.1)	66 (36.1)
High (≥50 × 10^3/μL)	5 (4.8)	1 (4.5)	3 (5.3)	9 (4.9)
Missing	1 (1.0)	0	3 (5.3)	4 (2.2)
Antecedent hematologic disorder, n (%)	20 (19.2)	2 (9.1)	9 (15.8)	31 (16.9)
MDS	16 (80.0)	1 (50.0)	5 (55.6)	22 (12.0)
Other	4 (20.0)	1 (50.0)	4 (44.4)	9 (4.9)
Leukemia secondary to prior therapy, n (%)	5 (4.8)	0	7 (12.3)	12 (6.6)

Demographics and disease characteristics were summarized using the full analysis set, which comprised all registered patients from the safety cohort plus all randomized patients from the randomization cohort.

"Unknown" category includes missing data and data not allowed to be collected.

[a]One patient in the safety cohort was *FLT3* negative.

[b]Participants may have reported more than one cytogenetic risk status.

[c]WBC categories were determined based on previous research (Ozga et al. 2021[1])

AZA, azacitidine; BMI, body mass index; BSA, body surface area; ECOG, Eastern Cooperative Oncology Group; *FLT3*, FMS-like tyrosine kinase 3; GIL, gilteritinib; HAR, high allelic ratio; IRT, interactive response technology; ITD, internal tandem duplication; LAR, low allelic ratio; max, maximum; MDS, myelodysplastic syndrome; min, minimum; PS, performance status; TKD, tyrosine kinase domain; WBC, white blood cell.

Table S3. Subsequent AML therapy

	Total GIL+AZA (n=103)	Randomized GIL (n=22)	AZA (n=54)
Participants with subsequent AML therapy, n (%)			
No	78 (75.7)	13 (59.1)	24 (44.4)
Yes	25 (24.3)	9 (40.9)	30 (55.6)
If yes, relapse prior to subsequent AML therapy, n (%)			
No	12 (11.7)	2 (9.1)	17 (31.5)
Yes	11 (10.7)	5 (22.7)	12 (22.2)
Unknown	2 (1.9)	2 (9.1)	1 (1.9)
Regimen, n (%)			
Azacitidine	11 (10.7)	2 (9.1)	9 (16.7)
Decitabine	2 (1.9)	3 (13.6)	0
Low-dose cytarabine	1 (1.0)	3 (13.6)	0
Etoposide+cytarabine	1 (1.0)	0	0
Other (all)	18 (17.5)	6 (27.3)	26 (48.1)
FLT3 inhibitor	4 (3.9)	2 (9.1)	20 (37.0)
Gilteritinib	3 (2.9)	2 (9.1)	15 (27.8)
Gilteritinib+azacitidine	1 (1.0)	0	0
Quizartinib	0	0	2 (3.7)
Sorafenib	0	0	4 (7.4)
Sorafenib+azacitidine	0	0	1 (1.9)
Non-FLT3 inhibitor	16 (15.5)	5 (22.7)	11 (20.4)
Time to first subsequent AML therapy (months)			
n	25	9	30
Mean (SD)	8.7 (4.40)	9.6 (5.80)	6.2 (6.70)
Median (min, max)	8.8 (1, 16)	8.5 (2, 18)	5.0 (0, 35)
Response to subsequent AML therapy, n (%)			
CR	0	0	3 (5.6)

	Total GIL+AZA (n=103)	Randomized GIL (n=22)	AZA (n=54)
CRp	1 (1.0)	0	1 (1.9)
CRi	1 (1.0)	0	3 (5.6)
NA	13 (12.6)	7 (31.8)	13 (24.1)
Duration of subsequent AML therapy (months)			
n	25	9	30
Median (min, max)[a]	3.3 (0, 41)	26.0 (0, 41)	5.5 (0, 40)
Duration of response to subsequent AML therapy (months)			
n	2	0	6
Median (min, max)[a]	5.5 (1, 10)	*NA*	4.0 (1, 15)

Proportions of patients with subsequent AML therapies were summarized in the safety analysis set, which comprised all patients from the randomization cohort and safety cohort who received ≥1 dose of study drug.

[a]"0" month is actually 1 day due to rounding.

AML, acute myeloid leukemia; AZA, azacitidine; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; CRp, complete remission with incomplete platelet recovery; FLT3, FMS-like tyrosine kinase 3; GIL, gilteritinib; max, maximum; min, minimum; NA, not applicable; SD, standard deviation.

Table S4. Rates of OS at 6, 12 and 24 months

OS (%) (95% CI)	Total GIL+AZA	Randomized GIL	AZA
6 months	63.2 (53.0, 71.8)	50.0 (28.2, 68.4)	64.4 (49.9, 75.6)
12 months	41.0 (31.1, 50.6)	40.9 (20.9, 60.1)	40.7 (27.3, 53.7)
24 months	18.8 (11.2, 27.9)	4.5 (0.3, 18.9)	12.9 (5.2, 24.3)

OS as a percentage of each cohort and 95% confidence intervals were estimated using the Kaplan-Meier method and Greenwood formula, using the full analysis set of patients (all registered patients from the safety cohort plus all randomized patients from the randomization cohort).

AZA, azacitidine; CI, confidence interval; GIL, gilteritinib; OS, overall survival.

Table S5. OS by subgroup of interest

	Total GIL+AZA			AZA				
	N	Events (%)	Median OS[a], months	N	Events (%)	Median OS[a], months	HR (95% CI)[b]	Nominal p value[c]
All	104	81 (77.9)	9.82	57	49 (86.0)	9.23	0.829 (0.554, 1.241)	0.363
Age								
<75 years	33	23 (69.7)	11.53	15	10 (66.7)	14.03	0.944 (0.445, 1.999)	0.880
≥75 years	71	58 (81.7)	9.49	42	39 (92.9)	8.57	0.759 (0.503, 1.146)	0.189
Sex								
Female	48	36 (75.0)	10.15	27	23 (85.2)	12.52	0.753 (0.443, 1.278)	0.293
Male	56	45 (80.4)	9.53	30	26 (86.7)	8.08	0.849 (0.523, 1.377)	0.506
Baseline ECOG PS								
0–1	54	40 (74.1)	13.17	37	32 (86.5)	9.95	0.765 (0.478, 1.225)	0.265
≥2	50	41 (82.0)	9.00	20	17 (85.0)	6.11	0.713 (0.402, 1.263)	0.246
Risk group								
Favorable/ intermediate/unknown/missing cytogenetic risk	91	71 (78.0)	10.15	48	40 (83.3)	9.95	0.784 (0.531, 1.157)	0.220
Unfavorable cytogenetic risk or secondary AML	13	10 (76.9)	2.63	9	9 (100)	7.20	1.111 (0.449, 2.749)	0.820
Baseline *FLT3* mutation type								

	Total GIL+AZA			AZA				
	N	**Events (%)**	**Median OS[a], months**	**N**	**Events (%)**	**Median OS[a], months**	**HR (95% CI)[b]**	**Nominal p value[c]**
ITD without TKD	80	62 (77.5)	11.63	46	39 (84.8)	8.87	0.661 (0.440, 0.994)	0.047
ITD and TKD (D835/I836)	4	1 (25.0)	*NE*	2	2 (100)	29.34	0.474 (0.040, 5.681)	0.556
TKD (D835/I836) without ITD	19	17 (89.5)	3.02	9	8 (88.9)	9.26	2.456 (0.976, 6.179)	0.056
Baseline *FLT3* mutation status								
ITD AR ≥0.5	50	40 (80.0)	11.89	29	23 (79.3)	7.46	0.515 (0.299, 0.885)	0.016
ITD AR <0.5	34	23 (67.6)	12.55	19	18 (94.7)	13.37	0.846 (0.452, 1.581)	0.599
TKD	19	17 (89.5)	3.02	9	8 (88.9)	9.26	2.456 (0.976, 6.179)	0.056

Analysis of OS by subgroup was conducted in the full analysis set of patients, which comprised all registered patients from the safety cohort plus all randomized patients from the randomization cohort. HRs and p values were for comparison between GIL+AZA and AZA. Total GIL+AZA: combined GIL+AZA from both safety and randomized cohorts.

[a]Based on Kaplan-Meier estimates.

[b]The HR reported for all patients was based on stratified Cox proportional hazards model adjusting for age group per IRT, risk groups, and baseline *FLT3* mutation status, with potential of strata pooling. In each subgroup, the HR was estimated using unstratified Cox proportional hazards model. Assuming proportional hazards, a HR <1 is in favor of GIL+AZA arm.

[c]Based on Wald test.

AML, acute myeloid leukemia; AZA, azacitidine; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; *FLT3*, FMS-like tyrosine kinase 3; GIL, gilteritinib; HAR, high allelic ratio; HR, hazard ratio; IRT, interactive response technology; ITD, internal tandem duplication; LAR, low allelic ratio; NE, not estimable; OS, overall survival; PS, performance status; TKD, tyrosine kinase domain.

Table S6. Key baseline characteristics and demographics by subsequent AML therapy, before and after propensity score matching

Analysis stratification factors and ECOG PS		Randomized GIL+AZA		AZA		PSM randomized GIL+AZA[a]
		With subsequent AML therapy, n=23	Without subsequent AML therapy, n=65	With subsequent AML therapy, n=30	Without subsequent AML therapy, n=24	Without subsequent AML therapy, n=48
Age per IRT, n (%)	<75	10 (43.5)	17 (26.2)	6 (20.0)	8 (33.3)	15 (31.2)
	≥75	13 (56.5)	48 (73.8)	24 (80.0)	16 (66.7)	33 (68.8)
Cytogenetic risk group, n (%)	Favorable or intermediate or unknown or missing	20 (87.0)	57 (87.7)	23 (76.7)	22 (91.7)	43 (89.6)
	Unfavorable or secondary AML	3 (13.0)	8 (12.3)	7 (23.3)	2 (8.3)	5 (10.4)
Baseline *FLT3* mutation status, n (%)	ITD LAR (<0.5)	11 (47.8)	18 (27.7)	10 (33.3)	9 (37.5)	18 (37.5)
	ITD HAR (≥0.5)	9 (39.1)	34 (52.3)	14 (46.7)	13 (54.2)	24 (50.0)
	TKD	3 (13.1)	13 (20.0)	6 (20.0)	2 (8.3)	6 (12.5)
ECOG PS, n (%)	0–1	11 (47.8)	38 (58.5)	24 (80.0)	11 (45.8)	28 (58.3)

	≥2	12 (52.2)	27 (41.5)	6 (20.0)	13 (54.2)	20 (41.7)

[a]Forty-eight of the 65 patients from the randomized GIL+AZA arm who did not receive subsequent AML therapy were matched to the 24 patients in the AZA arm who did not receive subsequent AML therapy, using propensity score matching based on ECOG score at baseline and *FLT3* mutation status.

AML, acute myeloid leukemia; AZA, azacitidine; ECOG, Eastern Cooperative Oncology Group; *FLT3*, FMS-like tyrosine kinase 3; GIL, gilteritinib; HAR, high allelic ratio; IRT, interactive response technology; ITD, internal tandem duplication; LAR, low allelic ratio; PS, performance status; PSM, propensity score matched; TKD, tyrosine kinase domain.

Table S7. Summary of response rates and duration of response

	Total GIL+AZA (n=104)	Randomized GIL (n=22)	AZA (n=57)
Overall response (CRc+PR)			
Rate, n (%)	73 (70.2)	16 (72.7)	21 (36.8)
95% CI, %[a]	60.4, 78.8	49.8, 89.3	24.5, 50.7
Treatment difference, % (95% CI)[b]	32.7 (16.0, 49.3)	NA	NA
P value[b]	<0.001	NA	NA
Time to response, days			
Median (min, max)	30 (25, 202)	30 (28, 86)	51 (28, 113)
Duration of overall response[c], months			
Median (95% CI)	8.80 (5.06, 12.98)	3.65 (0.95, 6.87)	7.62 (0.95, 9.23)
Range[d]	<0.1+, 56.4+	<0.1+, 10.2	0.0, 14.1
Stratified analysis on age per IRT			
Log-rank test 2-sided p value	0.133	NA	NA
Wald test p value[e]	0.134	NA	NA

	Total GIL+AZA (n=104)	Randomized GIL (n=22)	AZA (n=57)
HR (95% CI)[e]	0.609 (0.319, 1.165)	NA	NA
CR			
Rate, n (%)	28 (26.9)	2 (9.1)	10 (17.5)
95% CI, %[a]	18.7, 36.5	1.1, 29.2	8.8, 29.9
Treatment difference, % (95% CI)[b]	9.1 (−5.2, 23.5)	NA	NA
P value[b]	0.194	NA	NA
Time to CR, days			
Median (min, max)	199 (29, 862)	87 (30, 143)	113 (29, 212)
Duration of CR[c], months			
Median (95% CI)	25.10 (7.39, *NE*)	NE (NE, NE)	8.25 (0.95, NE)
Range[d]	<0.1+, 49.7+	1.8+, 2.8+	<0.1+, 9.5+
Stratified analysis on age per IRT			
Log-rank test 2-sided p value	0.270	NA	NA
Wald test p value[e]	0.276	NA	NA
HR (95% CI)[e]	0.530 (0.169, 1.662)	NA	NA

	Total GIL+AZA (n=104)	Randomized GIL (n=22)	AZA (n=57)
CRh			
Rate, n (%)	10 (9.6)	5 (22.7)	1 (1.8)
95% CI, %[a]	4.7, 17.0	7.8, 45.4	0.0, 9.4
Treatment difference, % (95% CI)[b]	7.9 (0.0, 15.9)	NA	NA
P value[b]	0.059	*NA*	*NA*
Duration of CRh[c], months			
Median (95% CI)	6.77 (1.35, 8.80)	2.83 (1.87, 5.95)	8.08 (*NE*, *NE*)
Range[d]	0.2+, 8.8	1.9, 5.9	8.1, 8.1
Stratified analysis on age per IRT			
Log-rank test 2-sided p value	0.285	NA	NA
Wald test p value[e]	0.998	NA	NA
HR (95% CI)[e]	>999 (<0.001, *NE*)	NA	NA
CR/CRh			
Rate, n (%)	38 (36.5)	7 (31.8)	11 (19.3)
95% CI, %[a]	27.3, 46.6	13.9, 54.9	10.1, 31.9

	Total GIL+AZA (n=104)	Randomized GIL (n=22)	AZA (n=57)
Treatment difference, % (95% CI)[b]	17.1 (2.0, 32.2)	NA	NA
P value[b]	0.025	NA	NA
Time to best CR/CRh, days			
Median (min, max)	174 (29, 862)	56 (28, 338)	95 (29, 212)
Duration of CR/CRh[c], months			
Median (95% CI)	8.80 (6.77, 27.30)	2.83 (1.87, 5.95)	8.08 (0.95, 8.57)
Range[d]	<0.1+, 49.7+	1.8+, 5.9	<0.1+, 9.5+
Stratified analysis on age per IRT			
Log-rank test 2-sided p value	0.351	NA	NA
Wald test p value[e]	0.355	NA	NA
HR (95% CI)[e]	0.632 (0.239, 1.673)	NA	NA
CRc			
Rate, n (%)	65 (62.5)	12 (54.5)	16 (28.1)
95% CI, %[a]	52.5, 71.8	32.2, 75.6	17.0, 41.5
Treatment difference, % (95% CI)[b]	33.9 (17.8, 50.0)	NA	NA

	Total GIL+AZA (n=104)	Randomized GIL (n=22)	AZA (n=57)
P value[b]	<0.001	NA	NA
Time to CRc, days			
Median (min, max)	41 (28, 222)	31 (28, 116)	58 (29, 155)
Duration of CRc[c], months			
Median (95% CI)	10.91 (7.39, 21.03)	3.65 (0.89, 7.39)	8.25 (2.10, 14.09)
Range[d]	<0.1+, 54.5+	0.5, 7.4	<0.1+, 14.1
Stratified analysis on age per IRT			
Log-rank test 2-sided p value	0.323	NA	NA
Wald test p value[e]	0.330	NA	NA
HR (95% CI)[e]	0.667 (0.295, 1.508)	NA	NA

Response rates and duration of response were calculated based on the full analysis set, which comprised all registered patients from the safety cohort plus all randomized patients from the randomization cohort. Based on best response. CR/CRh: CR or CRh; CRc: CR, CRp, or CRi; response: CRc+PR. Time to response, CR, CR/CRh, or CRc was only evaluated for patients who achieved a response, CR, CR/CRh, or CRc, respectively.

[a]Using the exact method based on binomial distribution.

[b]Based on stratified Cochran-Mantel-Haenszel test. Stratification factor was age group per interactive response technology.

[c]Based on Kaplan-Meier estimates.

[d]Plus symbol indicates censored data.

[e]Based on Cox proportional hazards model adjusted by age group per IRT. Assuming proportional hazards, a HR <1 is in favor of the GIL+AZA arm.

AZA, azacitidine; CI, confidence interval; CR, complete remission; CR/CRh, complete remission/complete remission with partial hematological recovery; CRc, composite complete remission; CRi, complete remission with incomplete hematological recovery; CRp, complete remission with incomplete platelet recovery; GIL, gilteritinib; HR, hazard ratio; IRT, interactive response technology; NA, not applicable; NE, not estimable.

Table S8. TEAE rates and exposure-adjusted incidence

	Total GIL+AZA (n=103, PY=79.6)		Randomized GIL (n=22, PY=11.3)		AZA (n=54, PY=21.7)	
	n (%)	E (E/PY)	n (%)	E (E/PY)	n (%)	E (E/PY)
TEAE	103 (100)	2 995 (37.62)	22 (100)	523 (46.30)	52 (96.3)	646 (29.83)
Treatment-related[a] TEAE	92 (89.3)	1 016 (12.76)	18 (81.8)	165 (14.61)	34 (63.0)	196 (9.05)
GIL-related	87 (84.5)	795 (9.98)	18 (81.8)	165 (14.61)	NA	NA
AZA-related	88 (85.4)	848 (10.65)	NA	NA	34 (63.0)	196 (9.05)
Serious TEAE[b]	95 (92.2)	445 (5.59)	20 (90.9)	87 (7.70)	34 (63.0)	83 (3.83)
Treatment-related[a] serious TEAE[b]	57 (55.3)	141 (1.77)	7 (31.8)	17 (1.50)	13 (24.1)	26 (1.20)
GIL-related	51 (49.5)	119 (1.49)	7 (31.8)	17 (1.50)	NA	NA
AZA-related	43 (41.7)	99 (1.24)	NA	NA	13 (24.1)	26 (1.20)
TEAE leading to death	42 (40.8)	49 (0.62)	9 (40.9)	11 (0.97)	13 (24.1)	17 (0.79)
Treatment-related[a] TEAE leading to death	4 (3.9)	4 (0.05)	0	0	5 (9.3)	5 (0.23)
GIL-related	3 (2.9)	3 (0.04)	0	0	NA	NA
AZA-related	3 (2.9)	3 (0.04)	NA	NA	5 (9.3)	5 (0.23)

	Total GIL+AZA (n=103, PY=79.6)		Randomized GIL (n=22, PY=11.3)		AZA (n=54, PY=21.7)	
	n (%)	**E (E/PY)**	**n (%)**	**E (E/PY)**	**n (%)**	**E (E/PY)**
TEAE leading to withdrawal of treatment	48 (46.6)	75 (0.94)	11 (50.0)	17 (1.50)	12 (22.2)	21 (0.97)
GIL withdrawal	44 (42.7)	63 (0.79)	11 (50.0)	17 (1.50)	NA	NA
AZA withdrawal	44 (42.7)	61 (0.77)	NA	NA	12 (22.2)	21 (0.97)
Treatment-related[a] TEAE leading to withdrawal of treatment	15 (14.6)	21 (0.26)	1 (4.5)	1 (0.09)	4 (7.4)	5 (0.23)
GIL-related	13 (12.6)	15 (0.19)	1 (4.5)	1 (0.09)	NA	NA
AZA-related	7 (6.8)	10 (0.13)	NA	NA	4 (7.4)	5 (0.23)
TEAE leading to dose reduction	26 (25.2)	35 (0.44)	3 (13.6)	3 (0.27)	0	0
GIL reduction	22 (21.4)	27 (0.34)	3 (13.6)	3 (0.27)	NA	NA
AZA reduction	8 (7.8)	9 (0.11)	NA	NA	0	0
Treatment-related[a] TEAE leading to dose reduction	26 (25.2)	35 (0.44)	3 (13.6)	3 (0.27)	0	0
GIL-related	21 (20.4)	26 (0.33)	3 (13.6)	3 (0.27)	NA	NA
AZA-related	8 (7.8)	9 (0.11)	NA	NA	0	0
TEAE leading to dose interruption	80 (77.7)	331 (4.16)	14 (63.6)	32 (2.83)	12 (22.2)	26 (1.20)
GIL interruption	69 (67.0)	241 (3.03)	14 (63.6)	32 (2.83)	NA	NA

	Total GIL+AZA (n=103, PY=79.6)		Randomized GIL (n=22, PY=11.3)		AZA (n=54, PY=21.7)	
	n (%)	E (E/PY)	n (%)	E (E/PY)	n (%)	E (E/PY)
AZA interruption	62 (60.2)	201 (2.52)	NA	NA	12 (22.2)	26 (1.20)
Treatment-related[a] TEAE leading to dose interruption	55 (53.4)	162 (2.03)	11 (50.0)	19 (1.68)	6 (11.1)	12 (0.55)
GIL-related	46 (44.7)	108 (1.36)	11 (50.0)	19 (1.68)	NA	NA
AZA-related	33 (32.0)	82 (1.03)	NA	NA	6 (11.1)	12 (0.55)
Grade 3 or higher TEAE[c]	101 (98.1)	926 (11.63)	21 (95.5)	182 (16.11)	49 (90.7)	197 (9.10)
Grade 3 or higher[c] treatment-related[a] TEAE	77 (74.8)	408 (5.12)	12 (54.5)	64 (5.67)	27 (50.0)	96 (4.43)
GIL-related	70 (68.0)	326 (4.09)	12 (54.5)	64 (5.67)	NA	NA
AZA-related	70 (68.0)	354 (4.45)	NA	NA	27 (50.0)	96 (4.43)
Death[d]	80 (77.7)	80 (1.00)	22 (100)	22 (1.95)	49 (90.7)	49 (2.26)

TEAEs were summarized in the safety analysis set (all patients from the randomization cohort and safety cohort who received ≥1 dose of study drug). PY was the total duration of treatment exposure in a year. GIL+AZA was considered drug-related if either GIL and/or AZA was related. GIL+AZA was considered withdrawn if either GIL and/or AZA led to withdrawal of treatment.

[a]Possible or probable, as assessed by the investigator, or records where relationship is missing.

[b]Includes serious TEAEs upgraded by the sponsor based on review of the sponsor's list of “Always Serious” terms, if any such upgrade was done.

[c]A missing CTCAE grade is considered the maximum CTCAE grade.

[d]All reported deaths after the first study drug administration.

AZA, azacitidine; CTCAE, Common Terminology Criteria for Adverse Events; E, number of events; GIL, gilteritinib; NA, not applicable; PY, patient-year; TEAE, treatment-emergent adverse event.

Table S9. Common[a] TEAEs

Preferred Term[b]	Total GIL+AZA (n=103, PY=79.6)		Randomized GIL (n=22, PY=11.3)		AZA (n=54, PY=21.7)	
	n (%)	E (E/PY)	n (%)	E (E/PY)	n (%)	E (E/PY)
Neutropenia	35 (34.0)	129 (1.62)	3 (13.6)	22 (1.95)	17 (31.5)	36 (1.66)
Pyrexia	45 (43.7)	109 (1.37)	9 (40.9)	18 (1.59)	18 (33.3)	19 (0.88)
Anemia	38 (36.9)	82 (1.03)	7 (31.8)	13 (1.15)	18 (33.3)	30 (1.39)
Thrombocytopenia	37 (35.9)	79 (0.99)	4 (18.2)	11 (0.97)	12 (22.2)	16 (0.74)
Febrile neutropenia	40 (38.8)	73 (0.92)	4 (18.2)	10 (0.89)	12 (22.2)	14 (0.65)
Nausea	33 (32.0)	65 (0.82)	3 (13.6)	3 (0.27)	13 (24.1)	13 (0.60)
AST increased	25 (24.3)	63 (0.79)	4 (18.2)	9 (0.80)	3 (5.6)	3 (0.14)
Diarrhea	39 (37.9)	63 (0.79)	9 (40.9)	12 (1.06)	10 (18.5)	12 (0.55)
Constipation	40 (38.8)	57 (0.72)	5 (22.7)	7 (0.62)	13 (24.1)	16 (0.74)
ALT increased	21 (20.4)	55 (0.69)	3 (13.6)	5 (0.44)	5 (9.3)	6 (0.28)
Hypokalemia	25 (24.3)	53 (0.67)	4 (18.2)	7 (0.62)	11 (20.4)	17 (0.79)
Platelet count decreased	18 (17.5)	53 (0.67)	6 (27.3)	44 (3.90)	9 (16.7)	22 (1.02)
Pneumonia	32 (31.1)	53 (0.67)	7 (31.8)	12 (1.06)	9 (16.7)	14 (0.65)

Preferred Term[b]	Total GIL+AZA (n=103, PY=79.6)		Randomized GIL (n=22, PY=11.3)		AZA (n=54, PY=21.7)	
	n (%)	E (E/PY)	n (%)	E (E/PY)	n (%)	E (E/PY)
Edema peripheral	29 (28.2)	48 (0.60)	7 (31.8)	8 (0.71)	8 (14.8)	9 (0.42)
Vomiting	27 (26.2)	46 (0.58)	7 (31.8)	8 (0.71)	10 (18.5)	10 (0.46)
Asthenia	23 (22.3)	43 (0.54)	3 (13.6)	5 (0.44)	9 (16.7)	10 (0.46)
Decreased appetite	21 (20.4)	33 (0.41)	2 (9.1)	2 (0.18)	10 (18.5)	12 (0.55)
Blood creatinine increased	19 (18.4)	31 (0.39)	6 (27.3)	10 (0.89)	3 (5.6)	4 (0.18)
Septic shock	8 (7.8)	13 (0.16)	5 (22.7)	6 (0.53)	1 (1.9)	1 (0.05)

TEAEs were summarized in the safety analysis set (all patients from the randomization cohort and safety cohort who received ≥1 dose of study drug).

[a]Only TEAEs experienced by ≥20% of patients in either the total GIL+AZA, randomized GIL, or AZA arms are shown.

[b]Preferred Terms were based on MedDRA v23.0.

PY was the total duration of treatment exposure in a year. Sorting order: descending by the frequency (E/PY) of each TEAE in the total GIL+AZA arm; in the case of ties, alphabetical order by Preferred Term was applied.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AZA, azacitidine; E, number of events; GIL, gilteritinib; MedDRA, Medical Dictionary for Regulatory Activities; PY, patient-year; TEAE, treatment-emergent adverse event.

Table S10. Myeloid co-mutations at screening

	Total GIL and GIL+AZA (n=125)	AZA (n=54)
NPM1, n/N (%)	60/119 (50.4)	21/51 (41.2)
NPM1*+*DNMT3a, n/N (%)[a]	17/119 (14.3)	5/51 (9.8)
RAS*/*MAPK, n/N (%)[b]	27/119 (22.7)	3/51 (5.9)
BRAF	0	1/51 (2.0)
CBL	3/119 (2.5)	0
KRAS	1/119 (0.8)	1/51 (2.0)
NRAS	15/119 (12.6)	2/51 (3.9)
PTPN11	12/119 (10.1)	1/51 (2.0)
Other, n/N (%)	91/119 (76.5)	39/51 (76.5)
ABL1	0	0
ASXL1	12/119 (10.1)	7/51 (13.7)
BCOR	1/119 (0.8)	0
CEBPA	0	0
CSF3R	1/119 (0.8)	0
DDX41	0	0
DNMT3A	29/119 (24.4)	8/51 (15.7)
EZH2	1/119 (0.8)	0
GATA2	0	0
IDH1	7/119 (5.9)	3/51 (5.9)
IDH2	10/119 (8.4)	3/51 (5.9)
JAK2	0	0
KIT	0	2/51 (3.9)
PHF6	0	0
RUNX1	7/119 (5.9)	5/51 (9.8)
SETBP1	4/119 (3.4)	0

	Total GIL and GIL+AZA (n=125)	AZA (n=54)
SF3B1	11/119 (9.2)	10/51 (19.6)
SRSF2	19/119 (16.0)	3/51 (5.9)
STAG2	0	0
TET2	8/119 (6.7)	3/51 (5.9)
TP53	4/119 (3.4)	0
U2AF1	8/119 (6.7)	2/51 (3.9)
WT1	5/119 (4.2)	4/51 (7.8)

Myeloid co-mutations were summarized in the safety analysis set (all patients from the randomization cohort and safety cohort who received ≥1 dose of study drug).

GIL includes subjects who received at least one dose of GIL. AZA includes patients in the AZA arm.

"n (%)" data corresponds to positive responses at screening. Myeloid mutation status was analyzed at screening after dosing. If a sample was tested and variant frequency was not detectable or <0.027, mutation was negative. Otherwise, if variant frequency was ≥0.027, gene mutation was positive. Five subjects did not have a sample for screening visit.

[a]*NPM1+DNMT3a*: All patients who have both *"NPM1"* variant frequency ≥0.027 and *"DNMT3a"* variant frequency ≥0.027.

[b]*RAS/MAPK*: All patients who have at least one variant frequency ≥0.027 in any of the following genes*: "BRAF", "CBL", "KRAS", "NRAS", and "PTPN11".*

ABL, ABL proto-oncogene 1; *ASXL*, ASXL transcriptional regulator 1; AZA, azacitidine; *BCOR*, BCL6 corepressor; *BRAF*, v-raf murine sarcoma viral oncogene homolog B1; *CBL*, casitas B-lineage lymphoma; *CEBPA*, CCAAT enhancer binding protein alpha; *CSF3R*, colony stimulating factor 3 receptor; *DDX41*, DEAD-box helicase 41; *DNMT3a*, deoxyribonucleic acid methyltransferase 3 alpha; *EZH2*, enhancer of zeste 2 polycomb repressive complex 2 subunit; *GATA2*, GATA binding protein 2; GIL, gilteritinib; *IDH1*, isocitrate dehydrogenase (NADP(+)) 1; *IDH2*, isocitrate dehydrogenase (NADP(+)) 2; *JAK2*, Janus kinase 2; *KIT*, KIT proto-oncogene; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; *MAPK*, mitogen-activated protein kinase; *NPM1*, nucleophosmin 1; *NRAS*, neuroblastoma rat oncogene; *PHF6*, PHD finger protein 6; *PTPN11*, protein tyrosine phosphatase non-receptor type 11; *RAS*, rat sarcoma; *RUNX1*, RUNX family transcription factor 1; *SETBP1*, SET

binding protein 1; *SF3B1*, splicing factor 3b subunit 1; *SRSF2*, serine and arginine rich splicing factor 2; *STAG2*, STAG2 cohesin complex component; *TET2*, tet methylcytosine dioxygenase 2; TP53, tumor protein p53; *U2AF1*, U2 small nuclear RNA auxiliary factor 1; *WT1*, WT1 transcription factor.

Table S11. *FLT3* mutation type and status at baseline and relapse

***FLT3* mutation type** **Treatment arm**	**Patients, n (%)**	
	Baseline (n=178)	**Relapse (n=26)[a]**
Total GIL+AZA	n=102	n=16
ITD without TKD	79 (77.5)	3 (18.8)
TKD (D835/I836) without ITD	19 (18.6)	0
ITD with TKD (D835/I836)	4 (3.9)	0
Randomized GIL	n=22	n=5
ITD without TKD	17 (77.3)	0
TKD (D835/I836) without ITD	2 (9.1)	0
ITD with TKD (D835/I836)	3 (13.6)	0
Randomized AZA	n=54	n=5
ITD without TKD	44 (81.5)	1 (20.0)
TKD (D835/I836) without ITD	8 (14.8)	1 (20.0)
ITD with TKD (D835/I836)	2 (3.7)	0
TKD (D835/I836) with unknown ITD	0	1 (20.0)[b]
***FLT3* mutation status** **Treatment arm**	**Baseline (n=178)**	**Relapse (n=26)[a]**
Total GIL+AZA	n=102	n=16
ITD LAR (<0.5)	34 (33.3)	3
ITD HAR (≥0.5)	49 (48.0)	0
TKD (D835/I836)	19 (18.6)	0
Randomized GIL	n=22	n=5

ITD LAR (<0.5)	8 (36.4)	0
ITD HAR (≥0.5)	12 (54.5)	0
TKD (D835/I836)	2 (9.1)	0
Randomized AZA	n=54	n=5
ITD LAR (<0.5)	19 (35.2)	1
ITD HAR (≥0.5)	27 (50.0)	0
TKD (D835/I836)	8 (14.8)	2

FLT3 mutation type and status were calculated in the safety analysis set (all patients from the randomization cohort and safety cohort who received ≥1 dose of study drug).

Percentages are calculated based on the number of patients in each treatment arm with a tested sample available.

[a]*FLT3* mutation type and status were analyzed for 26 patients who relapsed after achieving CRc or PR and had a tested sample available at the time of relapse with sufficient material to conduct *FLT3* testing.

[b]One patient at relapse tested positive for TKD but had insufficient sample to determine ITD status.

AZA, azacitidine; CRc, composite complete remission; *FLT3*, FMS-like tyrosine kinase 3; GIL, gilteritinib; ITD, internal tandem duplication; PR, partial remission; TKD, tyrosine kinase domain.

Table S12. Myeloid co-mutations at relapse

	Total GIL and GIL+AZA (n=125)	AZA (n=54)
NPM1, n/N (%)	8/23 (34.8)	2/5 (40.0)
NPM1*+*DNMT3A, n/N (%)[a]	2/23 (8.7)	1/5 (20.0)
RAS*/*MAPK, n/N (%)[b]	12/23 (52.2)	0/5 (0.0)
BRAF	0	0
CBL	0	0
KRAS	2/23 (8.7)	0
NRAS	9/23 (39.1)	0
PTPN11	3/23 (13.0)	0
Other, n/N (%)	19/23 (82.6)	3/5 (60.0)
ABL1	0	0
ASXL1	2/23 (8.7)	1/5 (20.0)
BCOR	0	0
CEBPA	1/23 (4.3)	0
CSF3R	1/23 (4.3)	0
DDX41	0	0
DNMT3A	5/23 (21.7)	1/5 (20.0)
EZH2	0	0
GATA2	1/23 (4.3)	0
IDH1	3/23 (13.0)	0
IDH2	4/23 (17.4)	0
JAK2	0	0
KIT	1/23 (4.3)	0
PHF6	0	0
RUNX1	0	1/5 (20.0)

	Total GIL and GIL+AZA (n=125)	AZA (n=54)
SETBP1	0	0
SF3B1	3/23 (13.0)	0
SRSF2	3/23 (13.0)	0
STAG2	0	0
TET2	0	0
TP53	0	0
U2AF1	1/23 (4.3)	0
WT1	5/23 (21.7)	0

Myeloid co-mutations were summarized in the safety analysis set (all patients from the randomization cohort and safety cohort who received ≥1 dose of study drug).

GIL includes subjects who received at least one dose of GIL. AZA includes patients in the AZA arm. "n (%)" data corresponds to positive responses at relapse. Myeloid mutation status was analyzed at relapse after dosing. If a sample was tested and variant frequency was not detectable or <0.027, mutation was negative. Otherwise, if variant frequency was ≥0.027, gene mutation was positive.

[a]*NPM1+DNMT3a*: All patients who have both *"NPM1"* variant frequency ≥0.027 and *"DNMT3a"* variant frequency ≥0.027.

[b]*RAS/MAPK*: All patients who have at least one variant frequency ≥0.027 in any of the following genes*: "BRAF", "CBL", "KRAS", "NRAS", and "PTPN11".*

ABL, ABL proto-oncogene 1; *ASXL*, ASXL transcriptional regulator 1; AZA, azacitidine; *BCOR*, BCL6 corepressor; *BRAF*, v-raf murine sarcoma viral oncogene homolog B1; *CBL*, casitas B-lineage lymphoma; *CEBPA*, CCAAT enhancer binding protein alpha; *CSF3R*, colony stimulating factor 3 receptor; *DDX41*, DEAD-box helicase 41; *DNMT3A*, deoxyribonucleic acid methyltransferase 3 alpha; *EZH2*, enhancer of zeste 2 polycomb repressive complex 2 subunit; *GATA2*, GATA binding protein 2; GIL, gilteritinib; *IDH1*, isocitrate dehydrogenase (NADP(+)) 1; *IDH2*, isocitrate dehydrogenase (NADP(+)) 2; *JAK2*, Janus kinase 2; *KIT*, KIT proto-oncogene; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; *MAPK*, mitogen-activated protein kinase; *NPM1*, nucleophosmin 1; *NRAS*, neuroblastoma rat oncogene; *PHF6*, PHD finger protein 6; *PTPN11*, protein tyrosine phosphatase non-receptor type 11; *RAS*, rat sarcoma; *RUNX1*, RUNX family transcription factor 1; *SETBP1*, SET

binding protein 1; *SF3B1*, splicing factor 3b subunit 1; *SRSF2*, serine and arginine rich splicing factor 2; *STAG2*, STAG2 cohesin complex component; *TET2*, tet methylcytosine dioxygenase 2; TP53, tumor protein p53; *U2AF1*, U2 small nuclear RNA auxiliary factor 1; *WT1*, WT1 transcription factor.

SUPPLEMENTARY REFERENCE

1. Ozga MP, Nicolet D, Mrózek K, et al. White blood cell count (WBC) levels are associated with molecular profiles and are independent outcome predictors in acute myeloid leukemia (AML) patients (Pts) (Alliance). Blood 2021;138(suppl 1):3369.