10-31-2019

Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML

Alexander E. Perl

Giovanni Martinelli

Jorge E. Cortes

Andreas Neubauer

Ellin Berman

See next page for additional authors

Authors

Alexander E. Perl, Giovanni Martinelli, Jorge E. Cortes, Andreas Neubauer, Ellin Berman, Stefania Paolini, Pau Montesinos, Maria R. Baer, Richard A. Larson, Celalettin Ustun, Francesco Fabbiano, Harry P. Erba, Antonio Di Stasi, Robert Stuart, Rebecca Olin, Margaret Kasner, Fabio Ciceri, Wen-Chien Chou, Nikolai Podoltsev, Christian Recher, Hisayuki Yokoyama, Naoko Hosono, Sung-Soo Yoon, Je-Hwan Lee, Timothy Pardee, Amir T. Fathi, Chaofeng Liu, Nahla Hasabou, Xuan Liu, Erkut Bahceci, and Mark J. Levis

Gilteritinib or Chemotherapy for Relapsed or Refractory *FLT3*-Mutated AML

A.E. Perl, G. Martinelli, J.E. Cortes, A. Neubauer, E. Berman, S. Paolini,
P. Montesinos, M.R. Baer, R.A. Larson, C. Ustun, F. Fabbiano, H.P. Erba,
A. Di Stasi, R. Stuart, R. Olin, M. Kasner, F. Ciceri, W.-C. Chou, N. Podoltsev,
C. Recher, H. Yokoyama, N. Hosono, S.-S. Yoon, J.-H. Lee, T. Pardee, A.T. Fathi,
C. Liu, N. Hasabou, X. Liu, E. Bahceci, and M.J. Levis

ABSTRACT

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Perl at the Perelman Center for Advanced Medicine 12 South, 3400 Civic Center Blvd., Philadelphia, PA 19104, or at alexander.perl@uphs.upenn.edu.

BACKGROUND
Patients with relapsed or refractory acute myeloid leukemia (AML) with mutations in the FMS-like tyrosine kinase 3 gene (*FLT3*) infrequently have a response to salvage chemotherapy. Gilteritinib is an oral, potent, selective FLT3 inhibitor with single-agent activity in relapsed or refractory *FLT3*-mutated AML.

METHODS
In a phase 3 trial, we randomly assigned adults with relapsed or refractory *FLT3*-mutated AML in a 2:1 ratio to receive either gilteritinib (at a dose of 120 mg per day) or salvage chemotherapy. The two primary end points were overall survival and the percentage of patients who had complete remission with full or partial hematologic recovery. Secondary end points included event-free survival (freedom from treatment failure [i.e., relapse or lack of remission] or death) and the percentage of patients who had complete remission.

RESULTS
Of 371 eligible patients, 247 were randomly assigned to the gilteritinib group and 124 to the salvage chemotherapy group. The median overall survival in the gilteritinib group was significantly longer than that in the chemotherapy group (9.3 months vs. 5.6 months; hazard ratio for death, 0.64; 95% confidence interval [CI], 0.49 to 0.83; P<0.001). The median event-free survival was 2.8 months in the gilteritinib group and 0.7 months in the chemotherapy group (hazard ratio for treatment failure or death, 0.79; 95% CI, 0.58 to 1.09). The percentage of patients who had complete remission with full or partial hematologic recovery was 34.0% in the gilteritinib group and 15.3% in the chemotherapy group (risk difference, 18.6 percentage points; 95% CI, 9.8 to 27.4); the percentages with complete remission were 21.1% and 10.5%, respectively (risk difference, 10.6 percentage points; 95% CI, 2.8 to 18.4). In an analysis that was adjusted for therapy duration, adverse events of grade 3 or higher and serious adverse events occurred less frequently in the gilteritinib group than in the chemotherapy group; the most common adverse events of grade 3 or higher in the gilteritinib group were febrile neutropenia (45.9%), anemia (40.7%), and thrombocytopenia (22.8%).

CONCLUSIONS
Gilteritinib resulted in significantly longer survival and higher percentages of patients with remission than salvage chemotherapy among patients with relapsed or refractory *FLT3*-mutated AML. (Funded by Astellas Pharma; ADMIRAL ClinicalTrials.gov number, NCT02421939.)

PATIENTS WITH ACUTE MYELOID LEUKEMIA (AML) whose disease is refractory to, or relapses after, induction chemotherapy have a dismal prognosis with standard chemotherapy.[1-4] FMS-like tyrosine kinase 3 (FLT3), a cytokine receptor tyrosine kinase that is expressed in early hematopoietic stem and progenitor cells, regulates their proliferation and differentiation.[5] *FLT3*-activating mutations occur in approximately 30% of patients with AML,[6] primarily as in-frame internal tandem duplications (ITD) within the juxtamembrane region or as missense point mutations in the tyrosine kinase domain (TKD).[7-9] In patients with AML, the presence of the *FLT3* ITD mutation adversely affects survival, both at diagnosis and on failure of the initial therapy.[10-12]

Several FLT3 tyrosine kinase inhibitors, either under development or approved for the treatment of AML, vary in kinase selectivity, potency, and clinical activity.[13-17] Midostaurin, a multitargeted inhibitor, is approved in combination with standard cytarabine and daunorubicin–based chemotherapy for patients with newly diagnosed *FLT3*-mutated AML.[18,19] However, for patients with relapsed or refractory AML, neither midostaurin nor lestaurtinib has conferred durable clinical benefit as a single agent.[13,14,20] Sorafenib showed clinical activity in patients with AML that was positive for the *FLT3* ITD mutation, but data from randomized trials that support its use in that context are scarce.[16] The FLT3 inhibitor quizartinib showed single-agent activity in patients with relapsed or refractory AML with the *FLT3* ITD mutation,[21] but responses were short-lived, probably owing to *FLT3* TKD mutations that emerged during treatment.[22] Similar resistance is seen with sorafenib.[23] Furthermore, quizartinib is myelosuppressive, probably owing to its activity against other hematopoietic tyrosine kinases, such as c-Kit.[24]

Gilteritinib is a new, highly selective, oral FLT3 inhibitor with activity against both *FLT3* mutation subtypes (ITD and TKD) and weak activity against c-Kit.[25,26] Gilteritinib also inhibits the tyrosine kinase AXL, which is implicated in FLT3 inhibitor resistance.[26,27] In a phase 1–2 study, single-agent gilteritinib therapy resulted in sustained inhibition of FLT3 autophosphorylation and, at doses of at least 80 mg per day, led to 41% of the patients with relapsed or refractory *FLT3*-mutated AML having a composite complete remission (complete remission with or without normal hematologic recovery); a starting dose of 120 mg per day was recommended for further study.[28] To investigate the clinical benefit of gilteritinib in the treatment of relapsed or refractory *FLT3*-mutated AML, we conducted a multicenter, randomized trial comparing gilteritinib with conventional salvage chemotherapy regimens.

METHODS

TRIAL DESIGN AND OVERSIGHT

The randomized, phase 3 ADMIRAL trial was conducted at 107 centers in 14 countries and was sponsored by Astellas Pharma. The trial was reviewed and approved by the institutional review board or ethics committee at each participating center and was conducted in accordance with the principles of the Declaration of Helsinki. All the patients provided written informed consent at enrollment.

Two authors who were employees of the sponsor designed the trial in collaboration with four academic authors. Investigators gathered and analyzed the data and submitted case-report forms to the sponsor, which performed data monitoring and statistical analyses. All the authors had access to the trial data and were involved in data interpretation. The authors and the sponsor vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol (available with the full text of this article at NEJM.org). The first and last authors wrote the manuscript, with additional writing and editorial assistance provided by medical writers who were funded by the sponsor.

PATIENTS

Patients 18 years of age or older were eligible if their disease was refractory to one or two cycles of conventional anthracycline-containing induction therapy or if they had hematologic relapse after a complete remission. Patients who were not candidates for anthracycline-containing induction regimens could participate if they had completed at least one cycle of alternative standard therapy that had been judged by the investigators as the appropriate choice to induce remission. At enrollment, patients' bone marrow and blood samples were screened for *FLT3* mutations by a central laboratory. Enrollment on the basis of local testing for the *FLT3* mutation was

permitted for patients with rapidly proliferative disease. Previous treatment with sorafenib or midostaurin as part of first-line induction, consolidation, or maintenance therapy was allowed.

FLT3 MUTATIONS

Patients were required to have *FLT3* ITD or TKD D835 or I836 mutations. The central laboratory (Invivoscribe) used a polymerase chain reaction–based assay that was modeled on published methods (LeukoStrat CDx).[29] *FLT3* mutations were considered to be present if the mutant-to-nonmutant allelic ratio was at least 0.05. The median *FLT3* ITD allelic ratio was established at 0.77, with a high *FLT3* ITD allelic ratio defined as 0.77 or greater and a low ratio as less than 0.77.

RANDOMIZATION AND TREATMENTS

Enrolled patients were randomly assigned in a 2:1 ratio by an interactive response technology system to receive once-daily gilteritinib (120 mg) or salvage chemotherapy. Randomization was stratified according to response to previous therapy and the chosen chemotherapy, which was selected by the local investigator before randomization from four possible options: mitoxantrone, etoposide, and cytarabine (MEC)[20]; fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin (FLAG-IDA)[30]; low-dose cytarabine; and azacitidine. MEC and FLAG-IDA were considered to be high-intensity regimens, and low-dose cytarabine and azacitidine were considered to be low-intensity regimens.

Gilteritinib or chemotherapy was administered in 28-day cycles. Patients receiving high-intensity chemotherapy were assessed for response on or after day 15 to determine the need for a second induction cycle; response was measured on day 1 of cycle 2. Gilteritinib or low-intensity chemotherapy was administered until documentation of a lack of clinical benefit or the occurrence of toxic effects or other discontinuation criterion as defined in the protocol. Responses to gilteritinib or low-intensity chemotherapy were assessed on day 1 of cycles 2 and 3 and every two to three cycles thereafter. No crossover between treatment groups was permitted. Patients in the gilteritinib group who did not have a protocol-defined composite complete remission at the dose of 120 mg per day could escalate the dose to 200 mg per day; those who had a response and proceeded to transplantation continued in the trial and could resume gilteritinib therapy 30 to 90 days after the transplantation if they had engraftment without relapse and no uncontrolled complications of transplantation.

END POINTS AND ASSESSMENTS

The two primary end points were overall survival and the percentage of patients who had complete remission with full or partial hematologic recovery. Key secondary end points were event-free survival (defined as freedom from treatment failure [i.e., relapse or lack of remission] or death) and the percentage of patients with complete remission. Complete remission with full or partial hematologic recovery was evaluated in an interim analysis in the gilteritinib group only and was summarized in the final analysis for both treatment groups. Overall survival, event-free survival, complete remission, and other end points were evaluated in the final analysis. Best response was noted at any postbaseline visit.

Treatment response was assessed with the use of modified International Working Group criteria (Table S1 in the Supplementary Appendix, available at NEJM.org).[31] Minimal residual disease was not assessed. Safety was assessed by evaluating the incidence of adverse events, including evaluation of vital signs, and results from clinical laboratory tests, electrocardiograms, and ophthalmologic examinations. Patient-reported outcomes (from the EuroQoL Group 5-Dimension 5-Level [EQ-5D-5L] instrument[32] and the Functional Assessment of Cancer Therapy–Leukemia[33] questionnaire) are not presented here. Next-generation sequencing for AML-associated mutations was performed in bone marrow or blood DNA samples obtained at baseline (Table S2). Expression of AXL (a receptor tyrosine kinase associated with drug resistance) was analyzed by means of flow cytometry. The postbaseline transfusion status (assessed 29 days after first dose until the last treatment dose) was evaluated in patients who received gilteritinib treatment for at least 84 days; transfusion independence was noted if no red-cell or platelet transfusions were administered for 56 consecutive days during the postbaseline period. (Additional information about *FLT3* mutations, treatments, dose modifications, and assessments is provided in the protocol and the Supplementary Appendix.)

STATISTICAL ANALYSIS

Assuming a 2:1 randomization ratio and that 10% of the patients would discontinue the trial, we calculated that a planned sample of 369 patients would provide the trial with approximately 90% power to detect a difference in the estimated median overall survival between the gilteritinib group (7.7 months) and the salvage chemotherapy group (5.0 months) (hazard ratio for death, 0.65) on the basis of 258 deaths at a one-sided alpha level of 0.0245. The first planned interim analysis — to evaluate the primary end point of the percentage of patients who had complete remission with full or partial hematologic recovery — occurred when approximately 141 patients in the gilteritinib group reached the time point of at least 112 days (four treatment cycles) after the receipt of first dose or after randomization; the interim evaluation of complete remission with full or partial hematologic recovery rate had no effect on trial conduct. The planned final analysis was performed when approximately 258 deaths had occurred.

Two-sided P values for the analysis of overall survival were determined with the use of the stratified log-rank test; the Kaplan–Meier method and the Greenwood formula were used to determine overall survival and event-free survival. The statistical analysis plan excluded provisions for multiplicity correction in the evaluation of secondary and other outcomes. These results are reported as point estimates and 95% confidence intervals without adjustment for multiplicity and should not be used to infer definitive treatment effects. Final efficacy and safety analyses were performed in the intention-to-treat population (all patients who underwent randomization) and the safety population (all patients who had received at least one dose of trial treatment), respectively. (Details regarding the statistical analysis are provided in the Supplementary Appendix.)

RESULTS

PATIENTS

From October 20, 2015, to February 20, 2018, a total of 625 patients entered screening. The event cutoff of 258 deaths, which triggered the final analysis, occurred on September 17, 2018; the database was locked on October 19, 2018. A total of 371 eligible patients underwent randomi-

zation; 247 were assigned to the gilteritinib group and 124 to the chemotherapy group (Fig. 1 and Table 1). Overall, 60.6% of the patients had relapsed AML (median duration of first remission, 6.0 months; range, 0.3 to 60.0), and 39.4% had primary refractory disease. Most patients (83.8%) had received previous induction therapy with anthracyclines but not FLT3 inhibitors (87.6%); 21 patients (5.7%) had received the *FLT3* inhibitor midostaurin. Receipt of previous hematopoietic-cell transplantation did not affect patient assignment to the high-intensity and low-intensity chemotherapy regimens. Nearly all the patients (94.1%) who received high-intensity chemotherapy received one treatment cycle. The median duration of low-intensity chemotherapy was 4 weeks (low-dose cytarabine, 4 weeks [range, 2 to 31]; azacitidine, 4 weeks [range, 1 to 26]). The median number of cycles of gilteritinib therapy received was 5 (range, 1 to 33).

At the time of this analysis, 110 patients remained alive and 38 were continuing therapy with gilteritinib. Common reasons for the discontinuation of gilteritinib were relapse, progression, or lack of efficacy (50.2%), death (14.6%), and adverse events (11.3%). Common reasons for the discontinuation of chemotherapy were relapse, progression, or lack of efficacy (39.5%), withdrawal by the patient (8.1%), physician decision (8.9%), and death (8.1%).

EFFICACY

The median duration of follow-up for overall survival was 17.8 months. The median overall survival was significantly longer among patients in the gilteritinib group than among those in the chemotherapy group (9.3 months vs. 5.6 months; two-sided P<0.001) (Fig. 2A). The hazard ratio for death with gilteritinib as compared with chemotherapy was 0.64 (95% confidence interval [CI], 0.49 to 0.83). The percentages of patients who were alive at 1 year were 37.1% in the gilteritinib group and 16.7% in the chemotherapy group. A consistent pattern of longer survival with gilteritinib than with chemotherapy was noted across multiple subgroups, including the high-intensity and low-intensity chemotherapy cohorts (Fig. 2B) and the high *FLT3* ITD allelic ratio subgroup (median overall survival, 7.1 vs. 4.3 months; hazard ratio for death, 0.49; 95% CI, 0.34 to 0.71). Among patients with primary
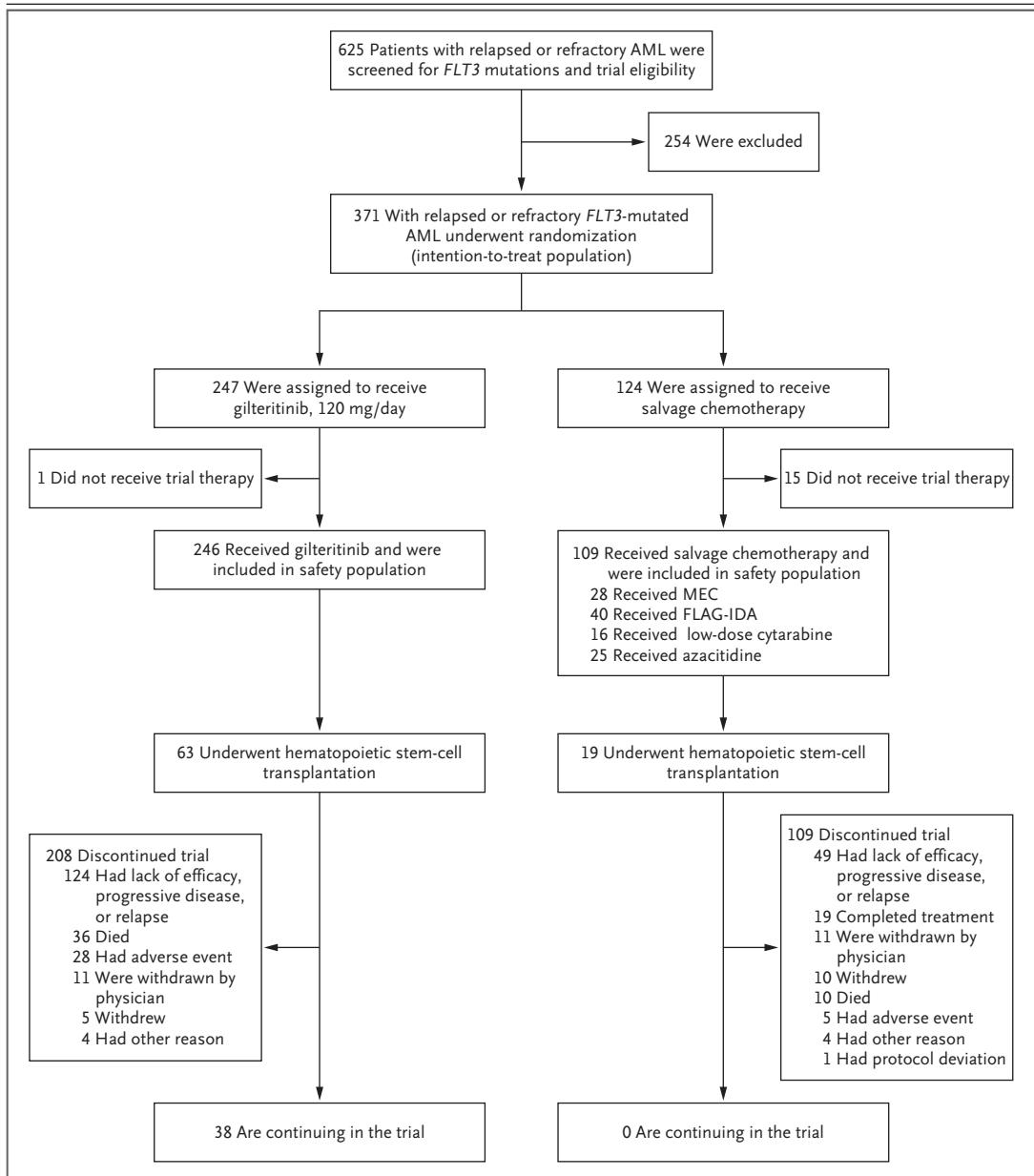
Figure 1. Screening, Randomization, and Treatment.

Of the 625 patients screened, 254 did not undergo randomization: 236 of 625 patients (37.8%) did not continue to randomization because inclusion or exclusion criteria were not met or because of absence of a mutation in the FMS-like tyrosine kinase 3 gene (*FLT3*), 10 patients (1.6%) had an adverse event, and 8 (1.3%) withdrew from the trial. A total of 25 of 63 patients in the gilteritinib group and all 19 patients in the salvage chemotherapy group who underwent hematopoietic stem-cell transplantation subsequently discontinued treatment. The safety population comprised all the patients who had received at least one dose of trial treatment. AML denotes acute myeloid leukemia; FLAG-IDA fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin; and MEC mitoxantrone, etoposide, and cytarabine.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	All Patients (N=371)	Gilteritinib (N=247)	Salvage Chemotherapy (N=124)
Age — yr			
Median	62.0	62.0	61.5
Range	19.0–85.0	20.0–84.0	19.0–85.0
Female sex — no. (%)	201 (54.2)	131 (53.0)	70 (56.5)
Cytogenetic risk status — no. (%)			
Favorable	5 (1.3)	4 (1.6)	1 (0.8)
Intermediate	271 (73.0)	182 (73.7)	89 (71.8)
Unfavorable	37 (10.0)	26 (10.5)	11 (8.9)
Unknown	58 (15.6)	35 (14.2)	23 (18.5)
Previous therapy for AML — no. (%)			
Anthracycline	311 (83.8)	205 (83.0)	106 (85.5)
FLT3 inhibitor	46 (12.4)	32 (13.0)	14 (11.3)
HSCT	74 (19.9)	48 (19.4)	26 (21.0)
Response to first-line therapy before enrollment — no. (%)†			
Relapse	225 (60.6)	149 (60.3)	76 (61.3)
Primary refractory disease without HSCT	146 (39.4)	98 (39.7)	48 (38.7)
Preselected salvage chemotherapy per IRT — no. (%)			
High-intensity chemotherapy	224 (60.4)	149 (60.3)	75 (60.5)
Low-intensity chemotherapy	147 (39.6)	98 (39.7)	49 (39.5)
FLT3 mutation subtype — no. (%)‡			
ITD only	328 (88.4)	215 (87.0)	113 (91.1)
TKD only	31 (8.4)	21 (8.5)	10 (8.1)
ITD and TKD	7 (1.9)	7 (2.8)	0

* The intention-to-treat population included all the patients who underwent randomization. Percentages may not total 100 because of rounding. AML denotes acute myeloid leukemia, HSCT hematopoietic stem-cell transplantation, ITD internal tandem duplication, and TKD tyrosine kinase domain.
† Response was based on findings from interactive response technology (IRT).
‡ Central laboratory confirmed the *FLT3* mutation status. Five patients (1.3%) had unconfirmed *FLT3* mutations; four patients (1.6%) were assigned to the gilteritinib group and one (0.8%) to the chemotherapy group.

refractory AML, the median overall survival was 10.4 months in the gilteritinib group and 6.9 months in the chemotherapy group (hazard ratio for death, 0.99; 95% CI, 0.63 to 1.55) (Table S3).

Although a higher percentage of patients underwent transplantation in the gilteritinib group than in the chemotherapy group (25.5% [63 of 247 patients] vs. 15.3% [19 of 124 patients]), the overall survival advantage for gilteritinib was also maintained when survival data were censored at the time of transplantation (hazard ratio for death, 0.58; 95% CI, 0.43 to 0.76) (Fig. S1).

Survival outcomes in patients who had been preselected to receive high-intensity chemotherapy or low-intensity chemotherapy and in those who had undergone transplantation previously are presented in Table S4.

The median event-free survival was 2.8 months in the gilteritinib group and 0.7 months in the chemotherapy group (hazard ratio for treatment failure or death, 0.79; 95% CI, 0.58 to 1.09) and did not differ significantly between the treatment groups (Fig. S2). Because the percentage of patients with composite complete remission in

A Overall Survival

Median Overall Survival (95% CI)

mo

Gilteritinib 9.3 (7.7–10.7)
Salvage Chemotherapy 5.6 (4.7–7.3)
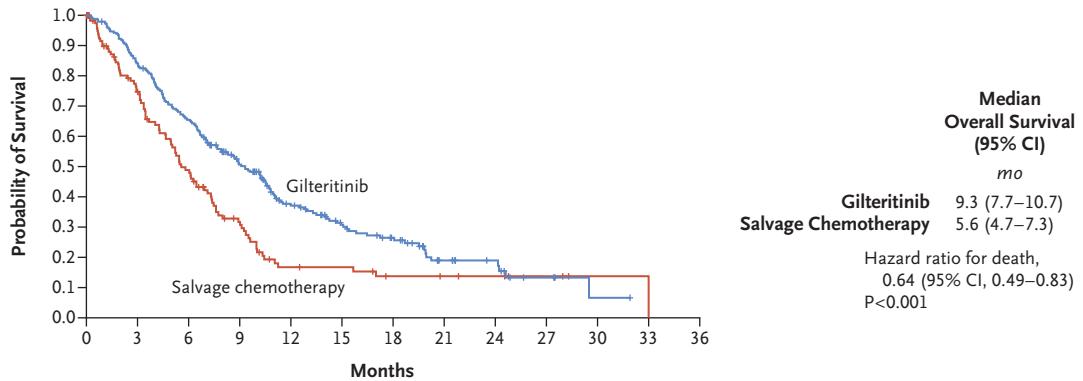
Hazard ratio for death,
0.64 (95% CI, 0.49–0.83)
P<0.001

No. at Risk

Gilteritinib	247	206	157	106	64	44	31	14	11	4	1	0	0
Salvage chemotherapy	124	84	52	29	13	12	8	7	5	3	1	0	0

B Subgroup Analysis of Overall Survival

Subgroup	Gilteritinib	Salvage Chemotherapy	Hazard Ratio for Death (95% CI)	
	no. of events/total no. of patients			
All patients	171/247	90/124		0.64 (0.49–0.83)
Age				
<65 yr	91/141	52/75		0.61 (0.43–0.86)
≥65 yr	80/106	38/49		0.64 (0.44–0.95)
Sex				
Male	86/116	40/54		0.72 (0.49–1.05)
Female	85/131	50/70		0.57 (0.40–0.82)
Race				
White	102/145	56/75		0.72 (0.52–1.00)
Black	13/14	6/7		0.54 (0.18–1.63)
Asian	42/69	20/33		0.34 (0.20–0.60)
Other or unknown	14/19	8/9		0.87 (0.36–2.12)
ECOG performance-status score				
0 or 1	138/206	78/105		0.60 (0.45–0.79)
≥2	33/41	12/19		0.87 (0.45–1.69)
Geographic region				
North America	88/114	42/52		0.72 (0.50–1.05)
Europe	43/68	32/43		0.67 (0.43–1.07)
Asia	40/65	16/29		0.38 (0.21–0.69)
FLT3 mutation type				
FLT3 ITD alone	145/215	81/113		0.62 (0.47–0.82)
FLT3 TKD alone	16/21	8/10		0.69 (0.29–1.64)
FLT3 ITD and *FLT3* TKD	6/7	0		NE (NE–NE)
Other	4/4	1/1		0.70 (0.06–7.92)
Previous use of *FLT3* inhibitor				
Yes	26/32	11/14		0.70 (0.35–1.44)
No	145/215	79/110		0.62 (0.47–0.82)
Cytogenetic risk status				
Favorable	3/4	1/1		0.70 (0.06–7.92)
Intermediate	119/182	63/89		0.60 (0.44–0.82)
Unfavorable	22/26	7/11		1.63 (0.69–3.85)
Unknown	27/35	19/23		0.46 (0.25–0.84)
Response to first-line therapy per IRT				
Relapse ≤6 mo after allogeneic HSCT	24/31	16/17		0.38 (0.20–0.75)
Relapse >6 mo after allogeneic HSCT	10/17	4/8		0.86 (0.26–2.80)
Primary refractory disease without HSCT	70/98	28/48		0.99 (0.63–1.55)
Relapse ≤6 mo after composite complete remission and no HSCT	47/67	28/34		0.49 (0.30–0.80)
Relapse >6 mo after composite complete remission and no HSCT	20/34	14/17		0.49 (0.25–0.98)
Preselected chemotherapy per IRT				
High intensity	96/149	52/75		0.66 (0.47–0.93)
Low intensity	75/98	38/49		0.56 (0.38–0.84)

Gilteritinib Better   Salvage Chemotherapy Better

ence, 10.6 percentage points; 95% CI, 2.8 to 18.4) (Table 2). The median duration of complete remission with full or partial hematologic recovery was 11.0 months in the gilteritinib group but could not be evaluated in the chemotherapy group because of censoring. The percentages of patients who had remission after an increase in the dose of gilteritinib (78 patients) or a decrease in the dose (58 patients) are shown in Table S5. When we excluded remissions that occurred after transplantation during the trial, the percentage of patients who had complete remission with full or partial hematologic recovery was 26.3% in the gilteritinib group and 15.3% in the chemotherapy group (risk difference, 10.9 percentage points; 95% CI, 2.4 to 19.5). Among patients with primary refractory AML, the percentage of patients who had complete remission with full or partial hematologic recovery was 32% (31 of 98 patients) in the gilteritinib group and 21% (10 of 48 patients) in the chemotherapy group (Table S3). The percentages of patients with a remission according to chemotherapy intensity and receipt or nonreceipt of previous transplantation are presented in Table S4.

Among patients with *FLT3* ITD mutations who had been randomly assigned to the gilteritinib group, 20.5% had a complete remission; among those who had been randomly assigned to chemotherapy, 9.7% had a complete remission (Table S6). Although the percentages of patients with complete remission were similar across the treatment groups among patients with *FLT3* TKD mutations, gilteritinib therapy resulted in similar percentages of complete remission among patients with *FLT3* TKD mutations alone (19.0%) and among those with *FLT3* ITD mutations alone (20.5%) (Table S6). Among patients treated with gilteritinib, the median overall survival was similar among those with *FLT3* ITD mutations alone (9.3 months) and those with *FLT3* TKD mutations alone (8.0 months). The most commonly co-mutated genes were *NPM1* (46.6%) and *DNMT3A* (31.0%). Longer survival was observed with gilteritinib than with chemotherapy across all cohorts of patients with co-mutations, particularly in the cohort of patients with double mutation (*DNMT3A* and *NPM1*). Baseline levels of AXL expression did not influence survival with gilteritinib. (Details are provided in Figs. S4 and S5.)

the low-intensity chemotherapy subgroup was 4% (2 of 49 patients), the event-free survival in the chemotherapy group was largely derived from the high-intensity chemotherapy subgroup. Because relapse events were defined on the basis of central review of bone marrow biopsy specimens, nearly all the patients who had a response to high-intensity chemotherapy and entered long-term follow-up had their data censored for event-free survival at 1 to 2 months after randomization, which limited the usefulness of the protocol-defined analysis of event-free survival. We performed a prespecified sensitivity analysis of event-free survival that included investigator-reported events during the long-term follow-up period (including the initiation of new antileukemic therapy), which showed event-free survival of 2.3 months in the gilteritinib group and 0.7 months in the chemotherapy group (hazard ratio, 0.50; 95% CI, 0.39 to 0.64) (Fig. S3).

The percentage of patients who had complete remission with full or partial hematologic recovery was 34.0% in the gilteritinib group and 15.3% in the chemotherapy group (risk difference, 18.6 percentage points; 95% CI, 9.8 to 27.4); the percentages of patients with complete remission were 21.1% and 10.5%, respectively (risk differ-

Overall, 197 of 247 patients (79.8%) who had been randomly assigned to the gilteritinib group

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

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

* Plus–minus values are means ±SD. Data shown are the best response at any time postbaseline. Data include 366 patients with central laboratory–confirmed *FLT3* mutations and 5 patients with *FLT3* mutations that were not confirmed by a central laboratory and were based on local laboratory testing. Response could not be evaluated (NE) in 14 patients (5.7%) in the gilteritinib group and in 49 (39.5%) in the salvage chemotherapy group. NA denotes not applicable, and ND not determined.

† Hazard ratios are shown for survival analyses, and risk differences (shown in percentage points) are shown for between-group differences in the percentages of patients. In the analysis of overall survival, the hazard ratio is for death. In the analysis of event-free survival, the hazard ratio is for treatment failure (i.e., relapse or lack of remission) or death.

‡ Composite complete remission was defined as the combination of complete remission, complete remission with incomplete hematologic recovery, and complete remission with incomplete platelet recovery.

§ Duration of remission was defined as the duration of complete remission with full or partial hematologic recovery.

were transfusion-dependent at randomization. A total of 68 of these 197 patients (34.5%) became transfusion-independent.

SAFETY

The median duration of exposure to gilteritinib and chemotherapy was 18 weeks (interquartile range, 9 to 34) and 4 weeks (interquartile range, 4 to 4), respectively; treatment exposure was 121.7 patient-years and 11.9 patient-years, respectively. The incidence of all exposure-adjusted adverse events, including those that were considered by the investigator to be drug-related, was higher in the chemotherapy group than in the gilteritinib group. Similar results were observed regarding adverse events that occurred during the first 30 days of treatment, except for eleva-

tions of the liver aminotransferase levels. (Details are provided in Tables S7 and S8.)

Common adverse events of grade 3 or higher in the gilteritinib group were febrile neutropenia (45.9%), anemia (40.7%), and thrombocytopenia (22.8%) (Table 3 and Table S9); these were also the most common adverse events of grade 3 or higher that were considered by the investigators to be related to gilteritinib therapy (Table S10). The incidence of exposure-adjusted adverse events of grade 3 or higher was 19.34 events per patient-year in the gilteritinib group and 42.44 events per patient-year in the chemotherapy group. Adverse events of grade 3 or higher that occurred during the first 30 days of treatment are presented in Table S8.

The incidence of exposure-adjusted serious

Table 3. Incidence of Adverse Events during Treatment That Occurred in at Least 20% of the Patients in Either Treatment Group (Safety Analysis Population).*

Event	Gilteritinib (N=246)			Salvage Chemotherapy (N=109)		
	Adverse Event of Any Grade	Grade ≥3 Adverse Event	Serious Adverse Event	Adverse Event of Any Grade	Grade ≥3 Adverse Event	Serious Adverse Event
	number of patients (percent)					
Febrile neutropenia	115 (46.7)	113 (45.9)	76 (30.9)	40 (36.7)	40 (36.7)	9 (8.3)
Anemia	116 (47.2)	100 (40.7)	8 (3.3)	38 (34.9)	33 (30.3)	0
Pyrexia	105 (42.7)	8 (3.3)	32 (13.0)	32 (29.4)	4 (3.7)	1 (0.9)
Alanine aminotransferase increased	103 (41.9)	34 (13.8)	13 (5.3)	10 (9.2)	5 (4.6)	0
Diarrhea	81 (32.9)	9 (3.7)	10 (4.1)	32 (29.4)	3 (2.8)	0
Aspartate aminotransferase increased	99 (40.2)	36 (14.6)	10 (4.1)	13 (11.9)	2 (1.8)	0
Hypokalemia	71 (28.9)	32 (13.0)	0	34 (31.2)	12 (11.0)	1 (0.9)
Constipation	76 (30.9)	2 (0.8)	0	16 (14.7)	0	0
Fatigue	70 (28.5)	6 (2.4)	4 (1.6)	14 (12.8)	2 (1.8)	1 (0.9)
Platelet count decreased	56 (22.8)	54 (22.0)	5 (2.0)	28 (25.7)	27 (24.8)	0
Cough	72 (29.3)	1 (0.4)	2 (0.8)	11 (10.1)	0	0
Thrombocytopenia	63 (25.6)	56 (22.8)	4 (1.6)	18 (16.5)	18 (16.5)	1 (0.9)
Headache	64 (26.0)	3 (1.2)	5 (2.0)	16 (14.7)	0	0
Peripheral edema	59 (24.0)	1 (0.4)	0	13 (11.9)	0	0
Vomiting	53 (21.5)	1 (0.4)	1 (0.4)	15 (13.8)	0	0
Dyspnea	58 (23.6)	10 (4.1)	10 (4.1)	7 (6.4)	3 (2.8)	2 (1.8)
Blood alkaline phosphatase increased	56 (22.8)	7 (2.8)	1 (0.4)	2 (1.8)	0	0

* The events shown are limited to adverse events that had a difference in incidence of more than 2 percentage points between the treatment groups. The safety population comprised all the patients who had received at least one dose of trial treatment.

adverse events, including those that were considered by the investigator to be drug-related, was 7.11 events per patient-year in the gilteritinib group and 9.24 events per patient-year in the chemotherapy group. The most common serious adverse events that were considered to be related to gilteritinib therapy were febrile neutropenia (23 patients [9.3%]), increase in the alanine aminotransferase level (11 patients [4.5%]), and increase in the aspartate aminotransferase level (10 patients [4.1%]). Drug-related adverse events leading to the discontinuation of gilteritinib occurred in 27 patients (11.0%); the most common events were elevated aspartate aminotransferase level (4 patients [1.6%]), elevated alanine aminotransferase level (3 [1.2%]), and pneumonia (3 [1.2%]) (Table S11). Prolonged corrected QT intervals

calculated with Fridericia's formula (QTcF intervals) that were considered to be possibly related to gilteritinib therapy occurred in 12 patients (4.9%), but only 1 patient (0.4%) had a maximum postbaseline increase in the mean QTcF interval of more than 500 msec. Dose reductions occurred in 6 patients who had a mean change from the baseline QTcF interval of more than 60 msec.

There were 251 deaths in the safety population of 355 patients, including 170 deaths among 246 patients (69.1%) in the gilteritinib group and 81 deaths among 109 patients (74.3%) in the chemotherapy group. In the intention-to-treat population, mortality at 30 days and at 60 days was 2.0% and 7.7%, respectively, in the gilteritinib group and 10.2% and 19.0%, respectively, in the chemotherapy group. Common fatal ad-

verse events in both groups were disease progression (30 patients [12.2%] in the gilteritinib group and 5 patients [4.6%] in the chemotherapy group) and infection (28 patients [11.4%] and 7 patients [6.4%], respectively). The most common fatal adverse events that were considered by the investigator to be drug-related in the gilteritinib group were pneumonia (3 patients [1.2%]), large intestine perforation (2 [0.8%]), and septic shock (2 [0.8%]); those in the chemotherapy group were sepsis (2 patients [1.8%]) and respiratory failure (2 [1.8%]) (Table S12).

DISCUSSION

Treatment options for patients with relapsed or refractory *FLT3*-mutated AML are largely limited to various salvage chemotherapy regimens, and there is no consensus regarding an approach. We found that in this population of patients, gilteritinib resulted in superior overall survival and percentages of remission as compared with salvage chemotherapy.

The efficacy of midostaurin plus chemotherapy for newly diagnosed *FLT3*-mutated AML showed the usefulness of targeting *FLT3*[19]; however, midostaurin has negligible activity in patients with relapsed or refractory AML.[14] Results from a similarly designed trial (QuANTUM-R) that compared quizartinib with salvage chemotherapy in patients with *FLT3* ITD–positive relapsed or refractory AML provide further evidence that targeting FLT3 prolongs survival as compared with salvage chemotherapy.[21] The present trial enrolled patients with *FLT3* ITD or *FLT3* TKD mutations. Although *FLT3* TKD mutations are uncommon at disease recurrence, they consistently and rapidly emerge during FLT3 inhibitor therapy to confer secondary resistance.[22,34] Gilteritinib had clinical activity in all studied *FLT3* mutation types. Not only were the percentages of patients with complete remission similar in the *FLT3* TKD and ITD cohorts, but the median overall survival in these two cohorts was also similar. Small sample sizes and challenges of multiple comparisons limit the statistical power and conclusiveness of subgroup analyses, including the subgroup analyses of *FLT3* TKD–positive relapsed or refractory AML (38 patients) and primary refractory AML (146 patients). Overall, gilteritinib showed a consistent survival benefit across many subgroups.

Our trial showed a survival advantage for FLT3-targeted therapy in patients with relapsed or refractory AML after data were censored for transplantation. Although gilteritinib therapy resulted in 63 patients being able to undergo transplantation, the contribution of the transplantation to the survival benefit from gilteritinib is difficult to assess. Although long-term survival after transplantation appeared to be associated with resumption of gilteritinib therapy, many factors may have contributed to this observation; we therefore caution against overinterpretation of this nonrandomized analysis. Regardless of transplantation, few patients with long-term survival were observed in either treatment group. Trials of gilteritinib as part of first-line induction or consolidation therapy and as postconsolidation or posttransplantation maintenance therapy (ClinicalTrials.gov numbers, NCT02927262, NCT02997202, and NCT02752035) are under way to assess the role of timing of anti-FLT3 intervention in improving treatment outcomes.

A limitation is that our trial design provided an imperfect estimate of response duration in the chemotherapy group for the comparison of event-free survival. In addition, enrollment occurred before widespread use of midostaurin in first-line chemotherapy, which could plausibly generate resistance to FLT3-targeted therapy and subsequently alter gilteritinib activity. Evidence suggests that mutational activation of RAS–RAF and related mitogen-associated protein kinase signaling frequently underlies secondary clinical resistance to gilteritinib,[35] but the causes of primary resistance require further investigation.

In conclusion, gilteritinib therapy led to higher percentages of patients with response and longer survival than salvage chemotherapy among patients with relapsed or refractory *FLT3*-mutated AML. The main toxic effect was myelosuppression. A small signal regarding hepatic toxic effects bears attention in future studies.

APPENDIX

The authors' full names and academic degrees are as follows: Alexander E. Perl, M.D., Giovanni Martinelli, M.D., Jorge E. Cortes, M.D., Andreas Neubauer, M.D., Ellin Berman, M.D., Stefania Paolini, M.D., Ph.D., Pau Montesinos, M.D., Maria R. Baer, M.D., Richard A. Larson, M.D., Celalettin Ustun, M.D., Francesco Fabbiano, M.D., Harry P. Erba, M.D., Ph.D., Antonio Di Stasi, M.D., Robert Stuart, M.D., Rebecca Olin, M.D., Margaret Kasner, M.D., Fabio Ciceri, M.D., Wen-Chien Chou, M.D., Ph.D., Nikolai Podoltsev, M.D., Christian Recher, M.D., Hisayuki Yokoyama, M.D., Naoko Hosono, M.D., Ph.D., Sung-Soo Yoon, M.D., Ph.D., Je-Hwan Lee, M.D., Ph.D., Timothy Pardee, M.D., Ph.D., Amir T. Fathi, M.D., Chaofeng Liu, Ph.D., Nahla Hasabou, M.D., Xuan Liu, Ph.D., Erkut Bahceci, M.D., and Mark J. Levis, M.D., Ph.D.

The authors' affiliations are as follows: the Abramson Cancer Center, University of Pennsylvania (A.E.P.), and Thomas Jefferson University (M.K.) — both in Philadelphia; Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Istituto Di Ricovero e Cura a Carattere Scientifico (IRCCS), Meldola (G.M.), L. and A. Seràgnoli Institute of Hematology, Bologna University Medical School, Bologna (S.P.), Ospedali Riuniti Villa Sofia-Cervello, Palermo (F.F.), and IRCCS San Raffaele Scientific Institute, Milan (F.C.) — all in Italy; University of Texas M.D. Anderson Cancer Center, Houston (J.E.C.); Universitätsklinikum Giessen und Marburg, Marburg, Germany (A.N.); Memorial Sloan Kettering Cancer Center, New York (E. Berman); Hospital Universitari i Politècnic La Fe, Valencia, and Centro de Investigación Biomédica en Red Cáncer (CIBERONC), Instituto Carlos III, Madrid — both in Spain (P.M.); University of Maryland Greenebaum Comprehensive Cancer Center (M.R.B.) and Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University (M.J.L.) — both in Baltimore; University of Chicago, Chicago (R.A.L.), and Astellas Pharma, Northbrook (C.L., N. Hasabou, X.L., E. Bahceci) — both in Illinois; University of Minnesota, Minneapolis (C.U.); University of Alabama at Birmingham, Birmingham (H.P.E., A.D.S.); Hollings Cancer Center, Medical University of South Carolina, Charleston (R.S.); University of California, San Francisco, San Francisco (R.O.); National Taiwan University, Taipei City, Taiwan (W.-C.C.); Yale University School of Medicine, New Haven, CT (N.P.); Centre Hospitalier Universitaire de Toulouse, Institut Universitaire du Cancer de Toulouse Oncopole, Université Toulouse III Paul Sabatier, Toulouse, France (C.R.); Sendai Medical Center, National Hospital Organization, Sendai (H.Y.), and University of Fukui, Fukui (N. Hosono) — both in Japan; Seoul National University (S.-S.Y.) and Asan Medical Center, University of Ulsan College of Medicine (J.-H.L.) — both in Seoul, South Korea; Wake Forest Baptist Medical Center, Winston-Salem, NC (T.P.); and Massachusetts General Hospital, Harvard Medical School, Boston (A.T.F.).

REFERENCES

1. Litzow MR, Othus M, Cripe LD, et al. Failure of three novel regimens to improve outcome for patients with relapsed or refractory acute myeloid leukaemia: a report from the Eastern Cooperative Oncology Group. Br J Haematol 2010;148: 217-25.

2. Roboz GJ, Rosenblat T, Arellano M, et al. International randomized phase III study of elacytarabine versus investigator choice in patients with relapsed/refractory acute myeloid leukemia. J Clin Oncol 2014; 32:1919-26.

3. Ravandi F, Ritchie EK, Sayar H, et al. Vosaroxin plus cytarabine versus placebo plus cytarabine in patients with first relapsed or refractory acute myeloid leukaemia (VALOR): a randomised, controlled, double-blind, multinational, phase 3 study. Lancet Oncol 2015;16:1025-36.

4. Megías-Vericat JE, Martínez-Cuadrón D, Sanz MA, Montesinos P. Salvage regimens using conventional chemotherapy agents for relapsed/refractory adult AML patients: a systematic literature review. Ann Hematol 2018;97:1115-53.

5. Small D, Levenstein M, Kim E, et al. STK-1, the human homolog of Flk-2/Flt-3, is selectively expressed in CD34+ human bone marrow cells and is involved in the proliferation of early progenitor/stem cells. Proc Natl Acad Sci U S A 1994;91:459-63.

6. Ravandi F, Kantarjian H, Faderl S, et al. Outcome of patients with FLT3-mutated acute myeloid leukemia in first relapse. Leuk Res 2010;34:752-6.

7. Nakao M, Yokota S, Iwai T, et al. Internal tandem duplication of the flt3 gene found in acute myeloid leukemia. Leukemia 1996;10:1911-8.

8. Kiyoi H, Towatari M, Yokota S, et al. Internal tandem duplication of the FLT3 gene is a novel modality of elongation mutation which causes constitutive activation of the product. Leukemia 1998;12: 1333-7.

9. Yamamoto Y, Kiyoi H, Nakano Y, et al. Activating mutation of D835 within the activation loop of FLT3 in human hematologic malignancies. Blood 2001;97:2434-9.

10. Chevallier P, Labopin M, Turlure P, et al. A new Leukemia Prognostic Scoring System for refractory/relapsed adult acute myelogeneous leukaemia patients: a GOELAMS study. Leukemia 2011;25: 939-44.

11. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. N Engl J Med 2016;374:2209-21.

12. Wattad M, Weber D, Döhner K, et al. Impact of salvage regimens on response and overall survival in acute myeloid leukemia with induction failure. Leukemia 2017;31:1306-13.

13. Smith BD, Levis M, Beran M, et al. Single-agent CEP-701, a novel FLT3 inhibitor, shows biologic and clinical activity in patients with relapsed or refractory acute myeloid leukemia. Blood 2004;103: 3669-76.

14. Fischer T, Stone RM, Deangelo DJ, et al. Phase IIB trial of oral midostaurin (PKC412), the FMS-like tyrosine kinase 3 receptor (FLT3) and multi-targeted kinase inhibitor, in patients with acute myeloid leukemia and high-risk myelodysplastic syndrome with either wild-type or mutated FLT3. J Clin Oncol 2010;28:4339-45.

15. Cortes J, Perl AE, Döhner H, et al. Quizartinib, an FLT3 inhibitor, as monotherapy in patients with relapsed or refractory acute myeloid leukaemia: an open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol 2018;19:889-903.

16. Borthakur G, Kantarjian H, Ravandi F, et al. Phase I study of sorafenib in patients with refractory or relapsed acute leukemias. Haematologica 2011;96:62-8.

17. Galanis A, Ma H, Rajkhowa T, et al. Crenolanib is a potent inhibitor of FLT3 with activity against resistance-conferring point mutants. Blood 2014;123:94-100.

18. RYDAPT (midostaurin) prescribing information. East Hanover, NJ: Novartis (https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/rydapt.pdf).

19. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a *FLT3* mutation. N Engl J Med 2017;377:454-64.

20. Levis M, Ravandi F, Wang ES, et al. Results from a randomized trial of salvage chemotherapy followed by lestaurtinib for patients with FLT3 mutant AML in first relapse. Blood 2011;117:3294-301.

21. Cortes JE, Khaled SK, Martinelli G, et al. Quizartinib versus salvage chemotherapy in relapsed or refractory FLT3-ITD acute myeloid leukaemia (QuANTUM-R): a multicentre, randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2019;20:984-97.

22. Smith CC, Wang Q, Chin CS, et al. Validation of ITD mutations in FLT3 as a therapeutic target in human acute myeloid leukaemia. Nature 2012;485:260-3.

23. Man CH, Fung TK, Ho C, et al. Sorafenib treatment of FLT3-ITD(+) acute myeloid leukemia: favorable initial outcome and mechanisms of subsequent nonresponsiveness associated with the emergence of a D835 mutation. Blood 2012; 119:5133-43.

24. Galanis A, Levis M. Inhibition of c-Kit by tyrosine kinase inhibitors. Haematologica 2015;100(3):e77-e79.

25. Lee LY, Hernandez D, Rajkhowa T, et al. Preclinical studies of gilteritinib, a next-generation FLT3 inhibitor. Blood 2017; 129:257-60.

26. Mori M, Kaneko N, Ueno Y, et al. Gilteritinib, a FLT3/AXL inhibitor, shows antileukemic activity in mouse models of FLT3 mutated acute myeloid leukemia. Invest New Drugs 2017;35:556-65.

27. Park IK, Mishra A, Chandler J, Whitman SP, Marcucci G, Caligiuri MA. Inhibition of the receptor tyrosine kinase Axl impedes activation of the FLT3 internal tandem duplication in human acute myeloid leukemia: implications for Axl as a potential therapeutic target. Blood 2013; 121:2064-73.

28. Perl AE, Altman JK, Cortes J, et al. Selective inhibition of FLT3 by gilteritinib in relapsed or refractory acute myeloid leukaemia: a multicentre, first-in-human, open-label, phase 1-2 study. Lancet Oncol 2017;18:1061-75.

29. Murphy KM, Levis M, Hafez MJ, et al. Detection of FLT3 internal tandem duplication and D835 mutations by a multiplex polymerase chain reaction and capillary electrophoresis assay. J Mol Diagn 2003;5: 96-102.

30. Jackson G, Taylor P, Smith GM, et al. A multicentre, open, non-comparative phase II study of a combination of fludarabine phosphate, cytarabine and granulocyte colony-stimulating factor in relapsed and refractory acute myeloid leukaemia and de novo refractory anaemia with excess of blasts in transformation. Br J Haematol 2001;112:127-37.

31. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol 2003;21: 4642-9.

32. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727-36.

33. Cella D, Jensen SE, Webster K, et al. Measuring health-related quality of life in leukemia: the Functional Assessment of Cancer Therapy — Leukemia (FACT-Leu) questionnaire. Value Health 2012;15: 1051-8.

34. Smith CC, Lin K, Stecula A, Sali A, Shah NP. FLT3 D835 mutations confer differential resistance to type II FLT3 inhibitors. Leukemia 2015;29:2390-2.

35. McMahon CM, Ferng T, Canaani J, et al. Clonal selection with Ras pathway activation mediates secondary clinical resistance to selective FLT3 inhibition in acute myeloid leukemia. Cancer Discov 2019;9: 1050-63.

Copyright © 2019 Massachusetts Medical Society.