Efficacy and safety of second-generation FLT3 inhibitors in acute myeloid leukemia: A systematic review and meta-analysis of randomized controlled trials

WEI-TING LIN[1], CHIEN-MING CHAO[2], CHENG-YAO LIN[3-5], YA-TING HSU[6], SHENG-YEN HSIAO[5,7*] and TENG-SONG WENG[8*]

[1]Department of Orthopedics, Chi Mei Medical Center, Tainan 710033, Taiwan, R.O.C.; [2]Department of Intensive Care Medicine, Chi Mei Medical Center, Liouying, Tainan 736402, Taiwan, R.O.C.; [3]Department of Senior Welfare and Services, Southern Taiwan University of Science and Technology, Tainan 710301, Taiwan, R.O.C.; [4]Department of Environmental and Occupational Health, College of Medicine, National Cheng Kung University, Tainan 701401, Taiwan, R.O.C.; [5]Division of Hematology-Oncology, Department of Internal Medicine, Chi Mei Medical Center, Liouying, Tainan 736402, Taiwan, R.O.C.; [6]Division of Hematology, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan 704302, Taiwan, R.O.C.; [7]Department of Nursing, Chung Hwa University of Medical Technology, Tainan 717302, Taiwan, R.O.C.; [8]Department of Pharmacy, Chi Mei Medical Center, Liouying, Tainan 736402, Taiwan, R.O.C.

Received June 7, 2024; Accepted August 15, 2024

DOI: 10.3892/mco.2024.2791

Abstract. Acute myeloid leukemia (AML) is one of the most frequent forms of acute leukemia and the second most common leukemia subtype in adults. In 2020, the incidence of AML in the United States was estimated to be ~4 cases per 100,000 adults. The FMS-like tyrosine kinase 3 (*FLT3*) internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutation are major prognostic indicators of AML. They are more frequently observed in younger AML patients (aged <60 years), likely due to their association with *de novo*. Additionally, these mutations have a stronger negative impact on survival in younger patients. Therefore, quizartinib and gilteritinib are second-generation FLT3 inhibitors that are frequently applied for treating patients with AML. However, to the best of our knowledge, few studies have compared the efficacy of second-generation FLT3 inhibitors for AML treatment. Therefore, the present study conducted a comprehensive search for studies on the efficacy and safety of FLT3 inhibitors across PubMed, Embase, the Cochrane Library and ClinicalTrials.gov. The search criteria were limited to randomized controlled trials (RCTs). Subsequently, a meta-analysis was performed on a total of five randomized controlled trials, involving 1,543 participants in total, using a random-effects model. In each RCT, compared to the salvage chemotherapy used in the control group, the groups that received second-generation FLT3 inhibitors experienced significant improvements in overall survival (hazard ratio, 0.717; 95% CI, 0.604-0.850; P<0.001). In addition, overall survival was found to be consistent across the different types of second-generation FLT3 inhibitors used and different types of AML. The risks associated with a prolonged heart-rate corrected QT interval (QTc) interval were next evaluated. Compared with the salvage chemotherapy used in the control group, the second-generation FLT3 inhibitor group exhibited a significantly higher risk of having a prolonged QTc interval (odds ratio, 6.311; 95% CI, 3.061-13.013; P<0.001). In conclusion, these findings suggest that second-generation FLT3 inhibitors can improve the overall survival of patients with AML. However, QTc prolongation is a potential adverse effect that should be monitored.

Correspondence to: Mr. Teng-Song Weng, Department of Pharmacy, Chi Mei Medical Center, 201 Taikang Liuying District, Liouying, Tainan 736402, Taiwan, R.O.C.
E-mail: ws22222@gmail.com

Dr Sheng-Yen Hsiao, Division of Hematology-Oncology, Department of Internal Medicine, Chi Mei Medical Center, 201 Taikang Liuying District, Liouying, Tainan 736402, Taiwan, R.O.C.
E-mail: seedvirt@gmail.com

*Contributed equally

Key words: second-generation FMS-like tyrosine kinase 3 inhibitors, gilteritinib, quizartinib, overall survival, prolonged heart-rate corrected QT interval

Introduction

Acute myeloid leukemia (AML) is the most frequent form of acute leukemia and the second most common leukemia subtype in adults (1). In 2020, the incidence of AML in the United States was estimated to be ~4 cases per 100,000 adults (2). Over the past two decades, results from studies has deepened the understanding whilst providing valuable insights into the genomics and pathophysiology of AML. In turn, these insights

have assisted in improvements in prognostic assessment techniques, which have and contributed to the development of novel therapeutic strategies for AML, including the use of second-generation FLT3 inhibitors and venetoclax (targeting Bcl-2) (3,4). In particular, FMS-like tyrosine kinase 3 (*FLT3*) gene mutation has been identified to be a major prognostic indicator for AML (5,6).

Internal tandem duplications (ITDs) in the *FLT3* gene have been detected in ~25% newly diagnosed AML cases, with ~7% *FLT3* mutations manifest as tyrosine kinase domain (TKD) point mutations (7,8). FLT3-ITD mutations are associated with an increased risk of treatment resistance to chemotherapy, particularly in patients receiving chemotherapy without an FLT3 inhibitor. By contrast, individuals with FLT3-TKD mutations may have a lower disease burden at diagnosis and they exhibit a superior response to chemotherapy (4,9). However, this does not necessarily imply that FLT3-TKD mutations will not develop chemotherapy resistance. Previous studies have shown that although FLT3-TKD mutations may respond better to chemotherapy initially, resistance can still develop over time, particularly in the context of clonal evolution or the acquisition of additional mutations during the course of the disease (10,11).

FLT3 inhibitors are a class of tyrosine kinase inhibitors and are categorized as first- and second-generation inhibitors, with the inhibitors categorized on the basis of their specificity and potency against the kinase (9). Midostaurin and sorafenib are examples of first-generation FLT3 inhibitors, whereas quizartinib and gilteritinib are examples second-generation inhibitors. Second-generation inhibitors were designed with structural modifications to improve selectivity and efficacy against mutant FLT3. These inhibitors bind more specifically to the active or inactive conformations of the FLT3 kinase domain, particularly targeting FLT3-ITD and TKD mutations. Specifically, quizartinib is tailored to inhibit mutant FLT3 while minimizing off-target effects on other kinases, whereas gilteritinib is effective against both FLT3-ITD and resistance-conferring D835 mutations, which are common in relapsed/refractory AML (12-15). Quizartinib and gilteritinib are both second-generation FLT3 inhibitors used to treat FLT3-mutated AML, but they target different forms of the mutation. Quizartinib is a type II inhibitor, meaning it primarily targets the FLT3-ITD mutation in the inactive conformation of the FLT3 kinase. By contrast, gilteritinib is a type I inhibitor, which is effective against both FLT3-ITD and FLT3-TKD mutations in their active forms, providing broader activity and potentially reducing the likelihood of resistance due to TKD mutations (16).

To the best of our knowledge, only one study (17) demonstrated improved overall survival in patients with relapsed or refractory AML, highlighting the efficacy of second-generation FLT3 inhibitors for AML treatment. Therefore, the present meta-analysis was performed to compare the clinical efficacy of such second-generation inhibitors in patients with AML in terms of overall survival. Additionally, the safety profiles of second-generation FLT3 inhibitors in relation to cardiac disorders, anemia, neutropenia, thrombocytopenia, diarrhea and pneumonia were compared. For clinical practice, this study suggests that second-generation FLT3 inhibitors are the optimal choice for treating patients with FLT3-mutated AML.

Materials and methods

Study search and selection. A comprehensive search for relevant studies was conducted across multiple databases, including PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://ovidsp-dc1-ovid-com.lib.chimei.org.tw:8443/ovid-new-a/ovidweb.cgi), the Cochrane Library (https://www.cochranelibrary.com/), Clinicaltril (https://clinicaltrials.gov/) and Medline (https://www.nlm.nih.gov/medline/medline_overview.html), from inception until April 28, 2024. To identify relevant studies, the following key words were used: 'Quizartinib OR AC220', 'Gilteritinib OR ASP2215' and 'Acute Myeloid Leukemia'. The present study exclusively considered randomized controlled trials (RCTs) assessing the efficacy and safety of second-generation FLT3 inhibitors. Crenolanib was not considered for the present study due to the absence of randomized controlled trial data. The present meta-analysis strictly adhered to including only RCTs to ensure the reliability and validity of the results. Without RCTs, the efficacy and safety of crenolanib in comparison to other second-generation FLT3 inhibitors could not be accurately assessed. Details regarding the search strategy for the present systematic review and meta-analysis are provided in Table SI. In total, two authors (TSW and SYH) conducted a thorough, independent screening and assessment of each study. In cases of discrepancy regarding the inclusion of an article, a third author (CMC) was consulted until a consensus was reached.

Inclusion and exclusion criteria. The population, intervention, comparison and outcome (PICO) framework for the present meta-analysis was as follows: i) P, human participants with AML and FLT3 mutations; ii) I, treatment with second-generation FLT3 inhibitors; iii) C, control group; and iv) O, overall survival time, heart-rate corrected QT interval (QTc) prolongation, cardiovascular disorders, anemia, neutropenia, thrombocytopenia, diarrhea and pneumonia.

In addition, the reference lists of the relevant articles were manually reviewed to identify possible additional eligible papers. No language restrictions were applied. RCTs meeting the following criteria were included: i) Inclusion of patients with a diagnosis of AML; ii) use of a second FLT3 inhibitor as monotherapy or in combination with other chemotherapy as the intervention; iii) reporting study outcomes related to overall survival; and iv) reporting study outcomes related to QTc prolongation or cardiovascular disorders, anemia, neutropenia, thrombocytopenia, diarrhea and pneumonia.

The following studies were excluded from the present review and meta-analysis: i) non-RCTs; ii) studies focusing on pharmacokinetic and pharmacodynamic analyses; iii) *in vitro* or animal experimental studies; iv) studies lacking a control group; and v) studies with participant overlap with previously published trials.

Study quality and outcome assessment. To assess the methodological quality of the included studies, the Cochrane risk of bias tool for randomized trials (version 2, RoB 2, https://sites.

google.com/site/riskofbiastool/welcome/rob-2-0-tool) was employed. This tool can be used to evaluate study quality in the following six key domains: Randomization process; adherence to intervention; handling of missing outcome data; outcome measurement; selective reporting; and overall risk of bias (18).

In the present study, the primary outcome was the efficacy of second-generation FLT3 inhibitors in improving overall survival. The exclusion of RFS and DFS from the present primary analysis was primarily due to the lack of available data on these outcomes in the studies included. The secondary outcomes included the risks of cardiovascular events, such as atrial fibrillation, cardiac failure, cardiac arrest, myocardial infarction, acute myocardial infarction and prolonged QT interval on electrocardiogram. Additionally, common adverse events, such as anemia, neutropenia, thrombocytopenia, diarrhea, pneumonia and event-free survival, were also evaluated. Overall survival is defined as the time from the initiation of treatment until death from any cause. It considers only one endpoint-mortality. Event-free survival, on the other hand, is defined as the time from the initiation of treatment until the occurrence of any event that signifies treatment failure, such as relapse, progression of the disease or mortality from any cause (19). It captures a broader range of outcomes, including both death and significant clinical events that indicate the treatment is no longer effective. To account for cells with zero events and to facilitate calculations, 0 was substituted with the value of 0.5. The aforementioned outcomes were quantified using odds ratios (ORs) (20).

Data extraction and general guidelines. In total, two authors (TSW and SYH) independently performed data extraction. The following data were extracted from each study: i) Name of the first author; ii) publication year; and iii) participant demographics, including age, sample size, specific second-generation FLT3 inhibitor used in treatment, outcome measures, efficacy in terms of overall survival and data on the risk of cardiovascular events and QT prolongation on electrocardiogram. The present meta-analysis was performed adhering to the latest version of the PRISMA 2020 guidelines (21). The present study was registered in INPLASY under the registration no. INPLASY202450141. It was not required to obtain ethics review board approval or participant informed consent.

Statistical analysis. Because of the heterogeneity in the types of second-generation FLT3 inhibitors used across the included studies, a random-effects model was used for the present meta-analysis (22). The meta-analysis was conducted using the Comprehensive Meta-Analysis software (version 4; Biostat, Inc.). $P<0.05$ was considered to indicate a statistically significant difference.

The primary study outcome was quantified by estimating hazard ratios (HRs) with 95% CIs, whereas ORs with their corresponding 95% CIs were calculated to analyze the secondary outcomes. The heterogeneity among the studies was assessed using the I^2-values. I^2-values of 25, 50 and 75% were considered to indicate low, moderate and high heterogeneity, respectively (23).

In addition, subgroup analyses according to the type of AML and the specific second-generation FLT3 inhibitor used were performed. Meta-regression analyses were performed to investigate the association between the impact of treatment effects based on age and overall survival outcomes, which were determined by the aforementioned parameters. To ensure the reliability of the meta-analysis, sensitivity analyses were conducted using the one-study removal approach. In this approach, each trial is removed from the analysis to determine whether exclusion of any specific trial leads to a significant change in the summary effect size experienced a statistically significant alteration when any specific trial was excluded. This suggests that the exclusion of individual trials can notably impact the overall results (20). Potential publication bias was assessed using Comprehensive Meta-Analysis software (version 4; Biostat, Inc.) in accordance with the guidelines provided in the Cochrane Handbook for Systematic Reviews of Interventions (24). Funnel plots were created and visually examined. In this study, bias was assessed using funnel plots. Bias was defined as the asymmetry of the funnel plot, which would suggest that smaller studies with non-significant results were less likely to be published, leading to a potential overestimation of the treatment effect. A symmetrical funnel plot would indicate the absence of such bias (25).

Results

Study selection. Fig. 1 illustrates the PRISMA flowchart depicting the literature search process (15). After elimination of duplicate articles and exclusion of non-relevant articles through title and abstract screening, 17 articles remained. Among these, 12 were excluded for the following reasons: i) 1 was related to dose analysis (26); ii) 4 focused on pharmacokinetics (27-30); iii) 1 lacked the salvage chemotherapy control group, the commonly used regimens include low-dose cytarabine (LoDAC), mitoxantrone, etoposide and intermediate-dose cytarabine (MEC) or fludarabine, cytarabine and granulocyte colony-stimulating factor (G-CSF) with idarubicin (FLAG-IDA) (31); iv) 1 was a protocol study (32); v) 3 had overlapping participant populations (32-35); and vi) 1 included patients achieving the first complete remission (34). A total of 5 RCTs were included in the final analysis (37-41).

The meta-analysis incorporated five eligible RCTs, involving a collective cohort of 1,543 participants receiving second-generation FLT3 inhibitors. These participants encompassed individuals diagnosed with relapsed or refractory FLT3-ITD AML (37,40) or with *de novo* or secondary AML (38), in addition to those with newly diagnosed FLT3-mutated AML (39,41). The salvage chemotherapy regimens encompassed various treatment protocols, including mitoxantrone, etoposide and cytarabine; fludarabine, cytarabine, granulocyte colony-stimulating factor and idarubicin; low-dose cytarabine; and azacitidine. Detailed information from the retrieved trials is presented in Table I.

Quality assessment of included studies. Regarding the overall methodological quality of the included studies, the results revealed that 20.0% of the studies exhibited a low risk of bias, whereas 80.0% had some degree of bias but none were

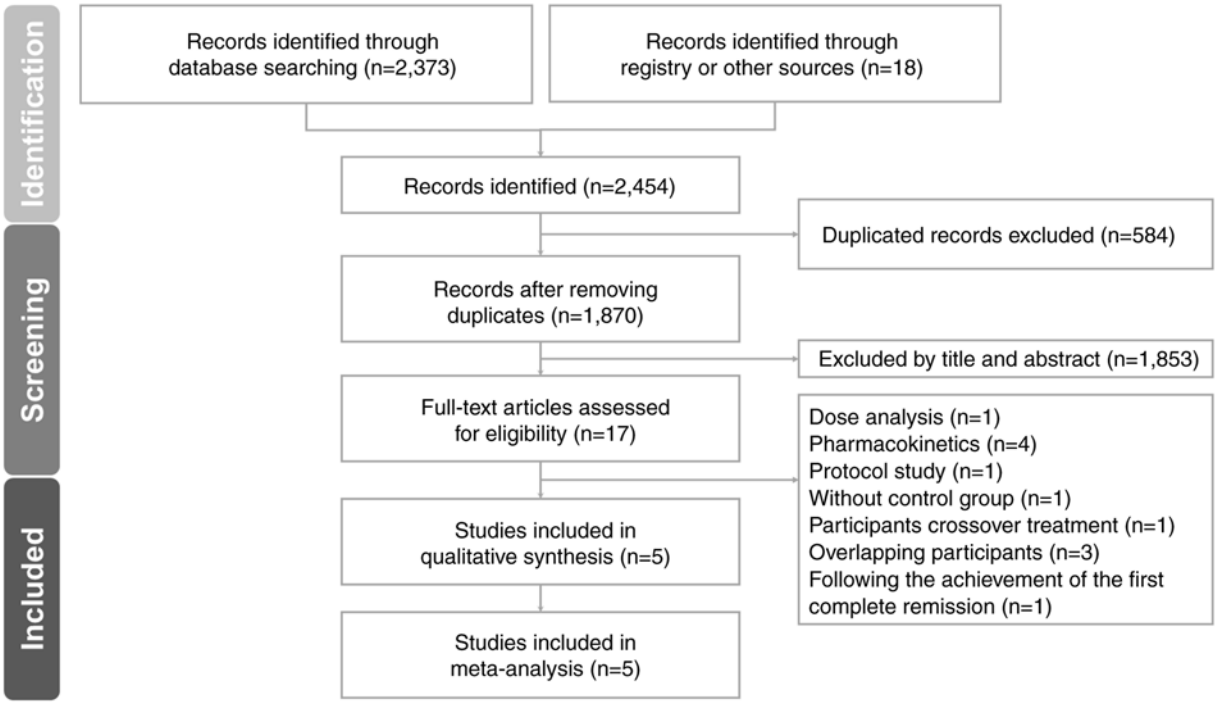

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flowchart of the study selection process.

deemed to have a high risk of bias (Fig. 2). In a comprehensive evaluation, three studies were categorized as having some risk of bias in outcome measurement because of their open-label designs (37,40,41). In addition, one study was classified as having some risk of bias because allocation concealment details were not provided (38). The findings of the risk of bias assessment are summarized in Table II.

Effect of second-generation FLT3 inhibitors on overall survival. In the pooled analysis of the five trials (Fig. 3), second-generation FLT3 inhibitors significantly improved overall survival (HR, 0.717; 95% CI, 0.604-0.850; P<0.001). However, low-to-moderate heterogeneity was noted. To address this, a sensitivity analysis was conducted by using the one-study removal method. Second-generation FLT3 inhibitors was revealed to consistently exert a significant effect on overall survival. Notably, the significance of these findings remained unchanged after the exclusion of any of the included studies (Fig. 4).

The included studies were subsequently categorized into two subgroups on the basis of the type of second-generation FLT3 inhibitor used, whereby one group consisted of studies with quizartinib use (30-32), whereas the other consisted of studies with gilteritinib use (40,41). The association between second-generation FLT3 inhibitors and overall survival remained consistent in both subgroups. Specifically, participants receiving quizartinib (HR, 0.707; 95% CI, 0.502-0.987; P=0.042) and those treated with gilteritinib (HR, 0.715; 95% CI, 0.551-0.927; P=0.011) had consistent HRs with overlapping 95% CIs (Fig. 5).

An additional subgroup analysis associated with the form of AML was subsequently performed. The newly diagnosed group experienced a significant overall survival benefit, indicating that the use of second-generation FLT3 inhibitors has a favorable effect in both clinically newly diagnosed and relapsed or refractory AML patients (HR, 0.796; 95% CI, 0.642-0.986; P=0.037). Similarly, the relapsed or refractory group (HR, 0.696; 95% CI, 0.578-0.837; P<0.001) and the other group (HR, 0.330; 95% CI, 0.142-0.769; P=0.010) experienced a significant overall survival effect (Fig. 6). A meta-regression analysis was next performed to assess the potential modification of the overall survival effects by age. Age exhibited a statistically significant but clinical trival correlation with overall survival (coefficient=-0.0058; P<0.001; Fig. 7). The funnel plot generated for the five included trials exhibited some asymmetry in the distribution of effect sizes (Fig. S1). However, Egger's regression test yielded P=0.450, indicating the absence of publication bias.

Risk of prolongation of QTc interval and cardiovascular disorders. The overall risks associated with a prolonged QTc interval and cardiovascular disorders were next examined. Compared to the salvage chemotherapy control group, in the second-generation FLT3 inhibitor group, the risk of a prolonged QTc interval was found to be significant (OR, 6.311; 95% CI, 3.061-13.013; P<0.001; Fig. 8). In addition, the risk of cardiovascular disorders in the second-generation FLT3 inhibitor group was observed to be comparable to that in the salvage chemotherapy control group (OR, 1.451; 95% CI, 0.538-3.911; P=0.462; Fig. S2).

Risk of anemia, neutropenia, thrombocytopenia, diarrhea and pneumonia. The risks of anemia, neutropenia, thrombocytopenia, diarrhea and pneumonia were next assessed. Compared to the second-generation FLT3 inhibitor group, the salvage chemotherapy control group showed a significantly higher risk of anemia. (OR, 1.350; 95% CI, 1.021-1.786;

Table I. Summary of the included randomized clinical trials investigating use of second-generation FLT3 inhibitors.

Author, year	Age, years	Population	Number patients	Second generation FLT 3	Control	Outcome measurement	(Refs.)
Cortes *et al*, 2019	56.0 (18-81)[a]	Relapsed or refractory FLT3-internal tandem duplications AML	Qui, 245; Salvage CT, 122	Qui, 20 OR 30 mg	Salvage CT	OS, EFS, AE and SAE	(37)
Dennis *et al*, 2021	77 (60-89)[a]	*De novo* and secondary AML	Qui, 72; Salvage CT, 71	Qui, 90 mg QD	Salvage CT	OS, AE and response rate	(38)
Erba *et al*, 2023	54.0±12.93[b]	Newly Diagnosed FLT3-mutated AML	Qui, 268; Salvage CT, 271	Qui, 40 mg QD	Salvage CT	OS, EFS, CR rate, AE and SAE	(39)
Perl *et al*, 2019	Gil 62 (20.0-84.0)[a]; Salvage CT 61.5 (19.0-85.0)[a]	Relapsed or Refractory FLT3-mutated AML	Gil, 247; Salvage CT, 124	Gil, 120 mg QD	Salvage CT	OS, EFS and AE	(40)
Wang *et al*, 2022	Gil + AZA, 77.4±5.6[b]; AZA, 76.7 ± 5.3[b]	Newly diagnosed FLT3 mutated AML	Gil + Salvage CT, 74; Salvage CT, 49	Gil, 120 mg QD + Salvage CT	Salvage CT	OS, EFS, response rates, AE and SAE	(41)

[a]Median (range); [b]mean ± SD. AML, acute myeloid leukemia; AE, Adverse events; CR, complete remission; CT, chemotherapy; EFS, event-free survival; RFS, relapse-free survival; OS, overall survival; SAE, serious adverse events; Qui, quizartinib; Gil, gilteritinib.

Table II. Comprehensive quality assessment of included studies as conducted using the Cochrane risk of bias 2 tool.

First author, year	Randomization process	Intervention adherence	Missing outcome data	Outcome measurement	Selective reporting	Overall risk of bias	(Refs.)
Cortes *et al*, 2019	S[a]	L	L	S[1]	L	S	(37)
Perl *et al*, 2019	S[a]	L	L	S[1]	L	S	(40)
Dennis *et al*, 2021	S[b]	L	L	L	L	S	(38)
Wang *et al*, 2022	S[a]	L	L	L	L	S	(41)
Erba *et al*, 2023	L	L	L	L	L	L	(39)

[a]Open-label study, where the participants were aware of the intervention allocated to them; [b]Allocation concealment details were not provided in the study. L, Low risk; S, Some concern.

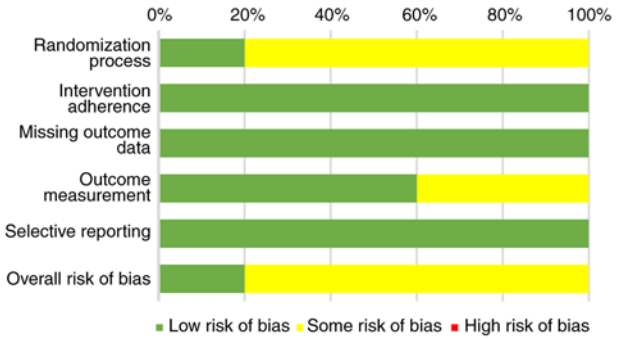

Figure 2. Overview of the quality assessment of included studies, conducted using the Cochrane risk of bias tool for randomized trials, version 2.

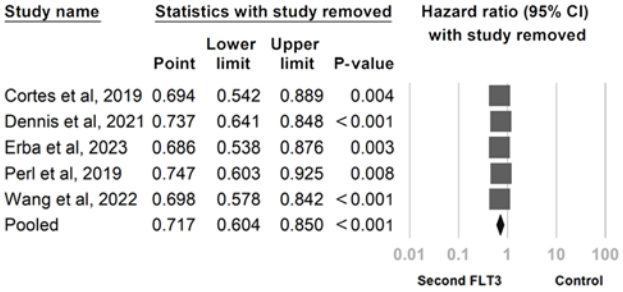

Figure 4. Sensitivity analysis of second-generation FLT3 inhibitors for the treatment of acute myeloid leukemia. The relative weight indicates each study's contribution to the overall effect in the meta-analysis. FLT3, FMS-like tyrosine kinase 3.

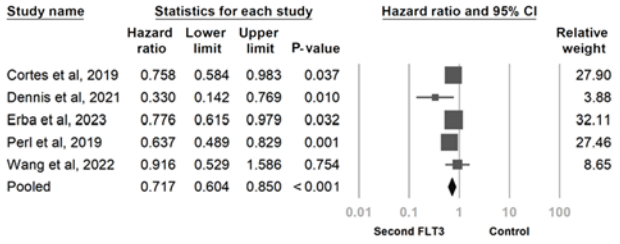

Figure 3. Summary of overall survival effect of second-generation FLT3 inhibitors. The relative weight indicates each study's contribution to the overall effect in the meta-analysis. FLT3, FMS-like tyrosine kinase 3.

P=0.035; Fig. S3). Additionally, the risk of neutropenia observed in the second-generation FLT3 inhibitor group was found to be similar to that in the salvage chemotherapy control group (OR, 1.380; 95% CI, 0.808-2.359; P=0.238; Fig. S4). The risk of thrombocytopenia was also comparable between the second-generation FLT3 inhibitor group and the salvage chemotherapy control group (OR, 1.321; 95% CI, 0.974-1.791; P=0.073; Fig. S5), whereas the incidence of diarrhea was comparable between the second-generation FLT3 inhibitor group and the salvage chemotherapy control group (OR, 1.315; 95% CI, 0.684-2.527; P=0.412; Fig. S6). No significant difference could be observed in the incidence of pneumonia between the second-generation FLT3 inhibitor group and the salvage chemotherapy control group (OR, 1.271; 95% CI, 0.725-2.227; P=0.403; Fig. S7).

Event free survival. Event-free survival was next assessed, which found that second-generation FLT3 inhibitors significantly improved event-free survival compared with that in the salvage chemotherapy control group (HR, 0.755; 95% CI, 0.582-0.980; P<0.05; Fig. S8).

Discussion

In the present meta-analysis, second-generation FLT3 inhibitors was found to significantly improve overall survival. In addition, the observed significant difference persisted in the sensitivity analyses. Various second-generation FLT3 inhibitors, such as Gilteritinib and Quizartinib, have been associated with improved overall survival. This improvement was consistent across different types of AML. Additionally, increasing age was correlated with improvements in overall survival. Although Hedges (42) addressed

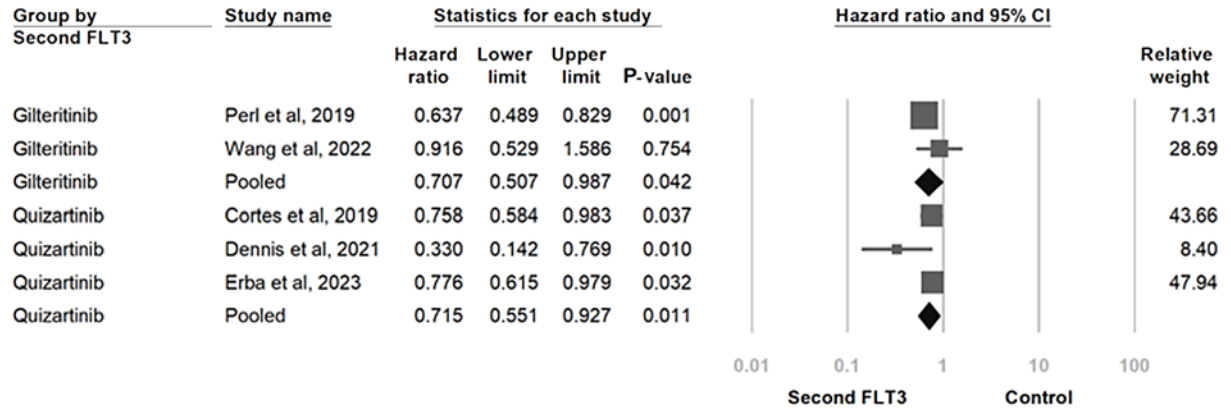

Figure 5. Subgroup analysis of overall survival effects following sorting by second-generation FLT3 Inhibitor. The relative weight indicates each study's contribution to the overall effect in the meta-analysis. FLT3, FMS-like tyrosine kinase 3.

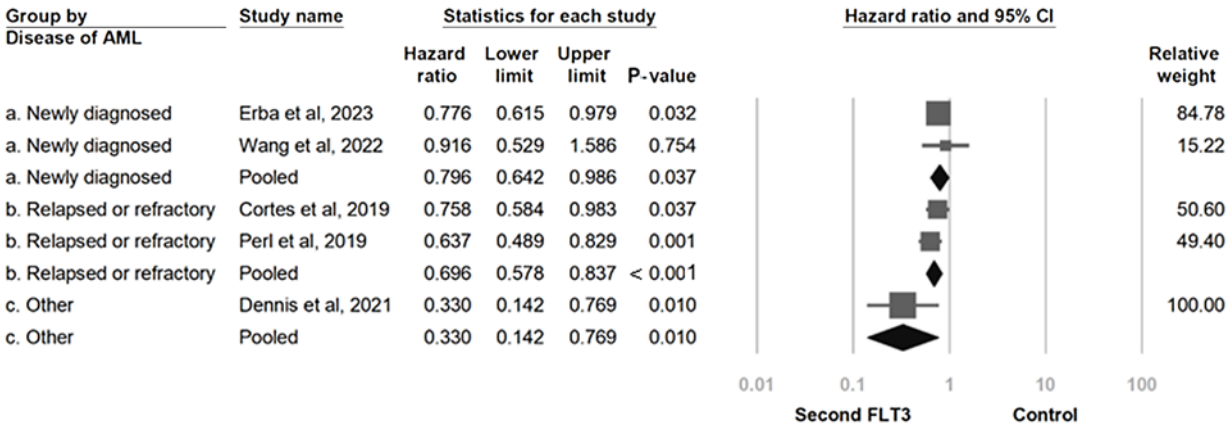

Figure 6. Subgroup analysis of overall survival effects stratified by the form of AML. The relative weight indicates each study's contribution to the overall effect in the meta-analysis. AML, acute myeloid leukemia.

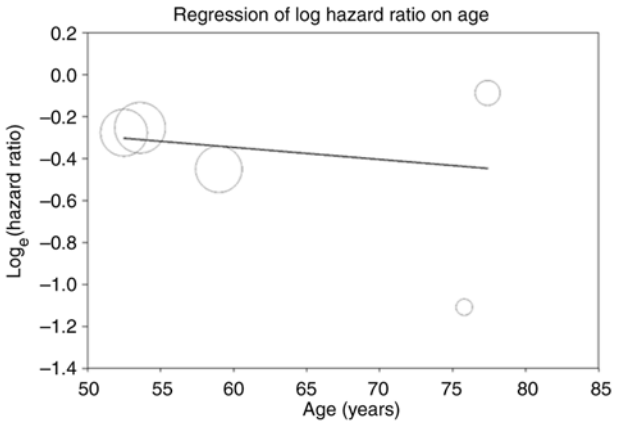

Figure 7. Meta-regression analysis of association between log HR and age. The sizes of each circle represent the relative weight of each study, and the base of the logarithm used was e.

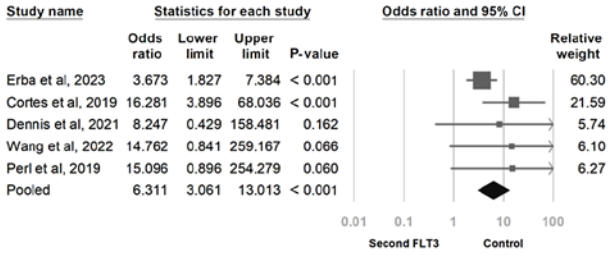

Figure 8. Comparison of the risk of prolonged QTc interval between second-generation FLT3 inhibitor group and control group. The relative weight indicates each study's contribution to the overall effect in the meta-analysis. FLT3, FMS-like tyrosine kinase 3.

the effect size and Deeks *et al* (20) explained the concept of low-to-moderate heterogeneity, to the best of our knowledge, the present study is the first to synthesize these insights in a systematic review and meta-analysis specifically focused on second-generation FLT3 inhibitors. By quantifying the heterogeneity observed across the included studies, the present analysis further supports the consistency of the therapeutic benefits of these inhibitors on overall survival across diverse patient populations and settings.

Previous meta-analyses have demonstrated improvements in overall survival to be associated with both first-generation inhibitors (such as sorafenib, lestaurtinib and midostaurin) and second-generation inhibitors (such as gilteritinib and quizartinib) (37-39,43). Mohebbi *et al* (17) previously reported that second-generation FLT3 inhibitors can improve overall survival in patients with relapsed or refractory AML (17). These findings are consistent with results from the

present study. However, the study by Mohebbi *et al* (17) on second-generation FLT3 inhibitors was limited by the early publication dates and two RCT studies by Cortes *et al* (37) and Perl *et al* (40). It is hoped that the present meta-analysis can bridge this a gap in the literature by providing an updated evaluation of the efficacy and safety of second-generation FLT3 inhibitors.

FLT3, belonging to the receptor tyrosine kinase family, exhibits a broad expression pattern in hematopoietic progenitor cells and is commonly overexpressed in AML blasts (44). Mutations in FLT3 are some the most prevalent genomic aberrations in AML, being detected in ~33.3% of newly diagnosed adults (45). FLT3 mutations can occur in the juxtamembrane domain, with such mutations commonly referred to as ITD mutations (FLT3-ITD) (46) or in the TKD (FLT3-TKD) (47,48). Second-generation FLT3 inhibitors, such as quizartinib, selectively inhibit FLT3 kinase activity, thereby preventing receptor autophosphorylation. This inhibition leads to the suppression of downstream FLT3 receptor signaling and arrest of the cell proliferation process that is dependent on FLT3-ITD (13). Gilteritinib, another second-generation FLT3 inhibitor, can also inhibit FLT3 receptor signaling and subsequently proliferation using a mechanism similar to that of quizartinib (49). Orally administered gilteritinib was reported to induce apoptosis in leukemic cells with FLT3-ITD mutations (50) and gilteritinib has been demonstrated to effectively target both FLT3 mutation subtypes (ITD and TKD) while both subtypes exhibit only weak activity against c-Kit (51,52). Although both gilteritinib and quizartinib are second-generation FLT3 inhibitors, they exhibit different levels of activity against the c-Kit receptor. Gilteritinib demonstrates relatively weak inhibition of c-Kit, with an IC_{50} of ~100 nM, meaning its impact on c-Kit is minimal, reducing the likelihood of marrow suppression. By contrast, quizartinib has stronger inhibitory activity against c-Kit, which may contribute to a higher risk of myelosuppression in clinical use (50).

In the separate subgroup analyses by use of gilteritinib or quizartinib in patients with different forms of AML, significant summary effect sizes were observed in both subgroups. This observation may be attributable to the efficacy of both treatments in improving overall survival in AML. Additionally, subgroup analyses were conducted for different forms of AML, including newly diagnosed, relapsed or refractory and other (referring to *de novo* or secondary) AML. Regardless of the AML subtype, second-generation FLT3 inhibitors were found to significantly improve overall survival. These findings suggest that second-generation FLT3 inhibitors led to a significant improvement in overall survival across multiple different AML subtypes. Furthermore, a statistically significant, though clinically trivial, correlation between patient age and overall survival in response to treatment was observed. These findings suggest that second-generation FLT3 inhibitors have greater effectiveness in improving overall survival in younger patients with AML with FLT3 mutations (coefficient=-0.0058 P<0.001).

Relapsed or refractory solid tumors in patients with advanced-stage cancer can potentially influence the physiological condition of the host. A possible reason is the disruption of the blood-brain barrier (52), allowing tumor cells to invade the brain. A previous study has reported that melanoma, skin, ovarian, and lung tumor cells may secrete hypothalamic hormones, pituitary hormones, steroids, catecholamines, serotonin, N-acetylserotonin, melatonin and leptin. The secretion of such neurohormonal modulators can ultimately disrupt the body's homeostasis (53). For instance, in AML, FLT3 mutations, particularly FLT3-ITD, result in the constitutive activation of downstream signaling pathways, such as the PI3K/Akt and STAT5 pathways, which are crucial for cell survival and proliferation (54,55). This activation can lead to the dysregulation of various cellular processes, much like how solid tumors disrupt homeostasis through the secretion of neurohormonal modulators.

QTc prolongation is the most frequent adverse event associated with the use of second-generation FLT3 inhibitors (26,56). The present study revealed the occurrence of QTc prolongation with the use of second-generation FLT3 inhibitors, to suggest that administration of second-generation FLT3 inhibitors may induce QTc prolongation due to elevated concentrations in patients with FLT3 mutations (57). Elevated concentrations of second-generation FLT3 inhibitors, such as quizartinib, can occur due to co-administration with cytochrome P450 3A4 inhibitors, which impede the drug's metabolism, leading to reduced clearance. This results in the accumulation of the drug in plasma, increasing its concentration over time. Such interactions are common, especially when patients are on multiple medications metabolized by the same pathway (58,59). At higher concentrations, FLT3 inhibitors (such as quizartinib) may block the human ether-a-go-go-related gene potassium channels, which are critical for cardiac repolarization. Inhibition of these channels disrupts the heart's electrical activity, leading to QTc prolongation. The risk of this effect is dose-dependent, meaning the higher the concentration of the drug, the more pronounced the QTc prolongation. This has been demonstrated in clinical studies of quizartinib, where elevated levels were directly associated with QTc interval changes. Therefore, greater attention should be given to such patients receiving these inhibitors (59,60). Additionally, an analysis of drug-related cardiovascular adverse events was conducted, but could not yield any significance. An analysis of common adverse events, such as anemia, neutropenia, thrombocytopenia, diarrhea, and pneumonia was also performed. A significant difference was found in only the incidence of anemia among patients treated with second-generation FLT3 inhibitors, likely due to the impact of these inhibitors on reducing platelet function (61). This finding highlights the importance of monitoring anemia in patients receiving second-generation FLT3 inhibitors. Additionally, the effect of second-generation FLT3 inhibitors on event-free survival compared with the control group was assessed. The results show that the use of second-generation FLT3 inhibitors significantly improved event-free survival, suggesting that second-generation FLT3 inhibitors can enhance event-free survival due to their activity against both FLT3 mutation subtypes (ITD and TKD).

The present study has several limitations. The second-generation FLT3 inhibitors used among the included trials differed, potentially contributing to heterogeneity. Therefore, the measurements were standardized using HRs, before applying

a random-effects model to combine the studies and perform subgroup analyses to address heterogeneity in accordance with the standard approach as recommended by the Cochrane Handbook (62,63). In addition, variability was observed in the age distribution among the trials, which may have influenced the estimated effects. Therefore, a meta-regression analysis was performed to investigate the presence of a linear relationship between age and overall survival. The present study also did not include the second-generation FLT3 inhibitor crenolanib due to the lack of randomized controlled trials. Future research should include RCTs involving crenolanib if data on such trials become available.

In summary, in the present study, second-generation FLT3 inhibitors, such as gilteritinib and quizartinib, were found to significantly improve overall survival, whereby age was statistically significant, though clinically trivial, correlation between patient age and overall survival in response to treatment. However, clinicians should remain aware of potential QTc prolongation when prescribing second-generation FLT3 inhibitors. Further investigations are warranted to explore the combined effect of crenolanib and second-generation FLT3 inhibitors, such as gilteritinib and quizartinib, on overall survival.

Acknowledgements

Not applicable.

Funding

The present study was funded by Chi Mei Medical Center, Liouying (grant no. CLFHR11133).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

SYH and YTH were responsible for designing the research and extracting the data. CMC, WTL and CYL conducted the statistical analysis and handled data visualization and interpretation. SYH and TSW prepared the initial draft of the manuscript. Both SYH and TSW performed critical revisions to the manuscript, focusing on essential intellectual content, and reviewed the data analysis. SYH and TSW confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Siegel RL, Miller KD and Jemal A: Cancer statistics, 2020. CA Cancer J Clin 70: 7-30, 2020.
2. Cancer Stat Facts: Leukemia-acute myeloid leukemia (AML). National Cancer Institute. https://seer.cancer.gov/statfacts/html/amyl.html. Accessed on September 1, 2024.
3. DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, Konopleva M, Döhner H, Letai A, Fenaux P, *et al*: Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med 383: 617-629, 2020.
4. Daver N, Schlenk RF, Russell NH and Levis MJ: Targeting FLT3 mutations in AML: Review of current knowledge and evidence. Leukemia 33: 299-312, 2019.
5. Kottaridis PD, Gale RE, Frew ME, Harrison G, Langabeer SE, Belton AA, Walker H, Wheatley K, Bowen DT, Burnett AK, *et al*: The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: Analysis of 854 patients from the United Kingdom medical research council AML 10 and 12 trials. Blood 98: 1752-1759, 2001.
6. Thiede C, Steudel C, Mohr B, Schaich M, Schäkel U, Platzbecker U, Wermke M, Bornhäuser M, Ritter M, Neubauer A, *et al*: Analysis of FLT3-activating mutations in 979 patients with acute myelogenous leukemia: Association with FAB subtypes and identification of subgroups with poor prognosis. Blood 99: 4326-4335, 2002.
7. Levis M: FLT3 mutations in acute myeloid leukemia: What is the best approach in 2013? Hematology Am Soc Hematol Educ Program 2013: 220-226, 2013.
8. Wander SA, Levis MJ and Fathi AT: The evolving role of FLT3 inhibitors in acute myeloid leukemia: Quizartinib and beyond. Ther Adv Hematol 5: 65-77, 2014.
9. Kennedy VE and Smith CC: FLT3 mutations in acute myeloid leukemia: Key concepts and emerging controversies. Front Oncol 10: 612880, 2020.
10. Schlenk RF, Döhner K, Krauter J, Fröhling S, Corbacioglu A, Bullinger L, Habdank M, Späth D, Morgan M, Benner A, *et al*: Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. N Engl J Med 358:1909-1918, 2008.
11. Eguchi M, Minami Y, Kuzume A and Chi S: Mechanisms underlying resistance to FLT3 inhibitors in acute myeloid leukemia. Biomedicines 8: 245, 2020.
12. Larrosa-Garcia M and Baer MR: FLT3 inhibitors in acute myeloid leukemia: Current status and future directions. Mol Cancer Ther 16: 991-1001, 2017.
13. Kampa-Schittenhelm KM, Heinrich MC, Akmut F, Döhner H, Döhner K and Schittenhelm MM: Quizartinib (AC220) is a potent second generation class III tyrosine kinase inhibitor that displays a distinct inhibition profile against mutant-FLT3, -PDGFRA and -KIT isoforms. Mol Cancer 12: 19, 2013.
14. Tarver TC, Hill JE, Rahmat L, Perl AE, Bahceci E, Mori K and Smith CC: Gilteritinib is a clinically active FLT3 inhibitor with broad activity against FLT3 kinase domain mutations. Blood Adv 4: 514-524, 2020.
15. Ge SS, Liu SB and Xue SL: Developments and challenges of FLT3 inhibitors in acute myeloid leukemia. Front Oncol 12: 996438, 2022.
16. The ASCO post: Tale of two FLT3 Inhibitors in AML:Gilteritinib and quizartinib. https://ascopost.com/issues/april-25-2019/tale-of-two-flt3-inhibitors-in-aml-gilteritinib-and-quizartinib. Accessed on September 5, 2024.
17. Mohebbi A, Shahriyary F, Farrokhi V, Bandar B and Saki N: A systematic review of second-generation FLT3 inhibitors for treatment of patients with relapsed/refractory acute myeloid leukemia. Leuk Res 141: 107505, 2024.
18. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, *et al*: RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ 366: l4898, 2019.
19. Verywell health: Event-free survival (EFS) after treatment. https://www.verywellhealth.com/event-free-survival-efs-2252150. Accessed on September 5, 2024.
20. Deeks JJ, Higgins JPT and Altman DG (eds): Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ and Welch VA (eds). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023.

21. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Hoffmann TC, *et al*: The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 372: n71, 2021.
22. Borenstein M, Hedges LV and Rothstein HR: Fixed-effect versus random-effects models. In: Introduction to Meta-Analysis. Wiley, Hoboken, NJ, 2009.
23. Higgins JP, Thompson SG, Deeks JJ and Altman DG: Measuring inconsistency in meta-analyses. BMJ 327: 557-560, 2003.
24. Page MJ, Higgins JPT and Sterne JAC: Chapter 13: Assessing risk of bias due to missing results in a synthesis. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ and Welch VA (eds). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane, 2020.
25. Sterne JAC, Sutton AJ, Ioannidis JPA, Terrin N, Jones DR, Lau J, Carpenter J, Rücker G, Harbord RM, Schmid, CH, *et al*: Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 343: d4002, 2011.
26. Cortes JE, Tallman MS, Schiller GJ, Trone D, Gammon G, Goldberg SL, Perl AE, Marie JP, Martinelli G, Kantarjian HM and Levis MJ: Phase 2b study of 2 dosing regimens of quizartinib monotherapy in FLT3-ITD-mutated, relapsed or refractory AML. Blood 132: 598-607, 2018.
27. James AJ, Smith CC, Litzow M, Perl AE, Altman JK, Shepard D, Kadokura T, Souda K, Patton M, Lu Z, *et al*: Pharmacokinetic profile of gilteritinib: A novel FLT-3 tyrosine kinase inhibitor. Clin Pharmacokinet 59: 1273-1290, 2020.
28. Li J, Holmes M, Kankam M, Trone D, Mendell J and Gammon G: Effect of food on the pharmacokinetics of quizartinib. Clin Pharmacol Drug Dev 9: 277-286, 2020.
29. Li J, Kankam M, Trone D and Gammon G: Effects of CYP3A inhibitors on the pharmacokinetics of quizartinib, a potent and selective FLT3 inhibitor, and its active metabolite. Br J Clin Pharmacol 85: 2108-2117, 2019.
30. Li J, Trone D, Mendell J, O'Donnell P and Cook N: A drug-drug interaction study to assess the potential effect of acid-reducing agent, lansoprazole, on quizartinib pharmacokinetics. Cancer Chemother Pharmacol 84: 799-807, 2019.
31. No authors listed: Gilteritinib plus azacitidine combination shows promise in newly diagnosed FLT3-mutated AML. Oncologist 26 (Suppl 1): S10, 2021.
32. Jaramillo S, Le Cornet L, Kratzmann M, Krisam J, Görner M, Hänel M, Röllig C, Wass M, Scholl S, Ringhoffer M, *et al*: Q-HAM: A multicenter upfront randomized phase II trial of quizartinib and high-dose Ara-C plus mitoxantrone in relapsed/refractory AML with FLT3-ITD. Trials 24: 591, 2023.
33. Hosono N, Yokoyama H, Aotsuka N, Ando K, Iida H, Ishikawa T, Usuki K, Onozawa M, Kizaki M, Kubo K, *et al*: Gilteritinib versus chemotherapy in Japanese patients with FLT3-mutated relapsed/refractory acute myeloid leukemia. Int J Clin Oncol 26: 2131-2141, 2021.
34. Perl AE, Larson RA, Podoltsev NA, Strickland S, Wang ES, Atallah E, Schiller GJ, Martinelli G, Neubauer A, Wang ES, *et al*: Follow-up of patients with R/R FLT3-mutation-positive AML treated with gilteritinib in the phase 3 ADMIRAL trial. Blood 139: 3366-3375, 2022.
35. Pulte ED, Norsworthy KJ, Wang Y, Xu Q, Qosa H, Gudi R, Przepiorka D, Fu W, Okusanya OO, Goldberg KB, *et al*: FDA approval summary: Gilteritinib for relapsed or refractory acute myeloid leukemia with a FLT3 mutation. Clin Cancer Res 27: 3515-3521, 2021.
36. NCT02927262: A Study of ASP2215 (Gilteritinib), administered as maintenance therapy following induction/consolidation therapy for subjects with FMS-like tyrosine kinase 3 (FLT3/ITD) acute myeloid leukemia (AML) in first complete remission. Journal, 2022.
37. Cortes JE, Khaled S, Martinelli G, Perl AE, Ganguly S, Russell N, Krämer A, Dombret H, Hogge D, Jonas BA, *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 20: 984-997, 2019.
38. Dennis M, Thomas IF, Ariti C, Upton L, Burnett AK, Gilkes A, Radia R, Hemmaway C, Mehta P, Knapper S, *et al*: Randomized evaluation of quizartinib and low-dose ara-C vs low-dose ara-C in older acute myeloid leukemia patients. Blood Adv 5: 5621-5625, 2021.
39. Erba HP, Montesinos P, Kim HJ, Patkowska E, Vrhovac R, Žák P, Wang PN, Mitov T, Hanyok J, Kamel YM, *et al*: Quizartinib plus chemotherapy in newly diagnosed patients with FLT3-internal-tandem-duplication-positive acute myeloid leukaemia (QuANTUM-First): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 401: 1571-1583, 2023.
40. Perl AE, Martinelli G, Cortes JE, Neubauer A, Berman E, Paolini S, Montesinos P, Baer MR, Larson RA, Ustun C, *et al*: Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. N Engl J Med 381: 1728-1740, 2019.
41. Wang ES, Montesinos P, Minden MD, Lee JH, Heuser M, Naoe T, Chou WC, Laribi K, Esteve J, Altman JK, *et al*: Phase 3 trial of gilteritinib plus azacitidine vs azacitidine for newly diagnosed FLT3mut+ AML ineligible for intensive chemotherapy. Blood 140: 1845-1857, 2022.
42. Hedges LV: Distribution theory for glass's estimator of effect size and related estimators. J Educ Stat 6: 107-128, 1981.
43. Majothi S, Adams D, Loke J, Stevens SP, Wheatley K and Wilson JS: FLT3 inhibitors in acute myeloid leukaemia: Assessment of clinical effectiveness, adverse events and future research-a systematic review and meta-analysis. Syst Rev 9: 285, 2020.
44. Carow CE, Levenstein M, Kaufmann SH, Chen J, Amin S, Rockwell P, Witte L, Borowitz MJ, Civin CI and Small D: Expression of the hematopoietic growth factor receptor FLT3 (STK-1/Flk2) in human leukemias. Blood 87: 1089-1096, 1996.
45. Papaemmanuil E, Gerstung M, Bullinger L, Gaidzik VI, Paschka P, Roberts ND, Potter NE, Heuser M, Thol F, Bolli N, *et al*: Genomic classification and prognosis in acute myeloid leukemia. N Engl J Med 374: 2209-2221, 2016.
46. Nakao M, Yokota S, Iwai T, Kaneko H, Horiike S, Kashima K, Sonoda Y, Fujimoto T and Misawa S: Internal tandem duplication of the flt3 gene found in acute myeloid leukemia. Leukemia 10: 1911-1918, 1996.
47. Yamamoto Y, Kiyoi H, Nakano Y, Suzuki R, Kodera Y, Miyawaki S, Asou N, Kuriyama K, Yagasaki F, Shimazaki C, *et al*: Activating mutation of D835 within the activation loop of FLT3 in human hematologic malignancies. Blood 97: 2434-2439, 2001.
48. Abu-Duhier FM, Goodeve AC, Wilson GA, Care RS, Peake IR, Reilly JT: Identification of novel FLT-3 Asp835 mutations in adult acute myeloid leukaemia. Br J Haematol 113: 983-988, 2001.
49. Inc. AP: Xospata (gilteritinib) tablets package insert. https://astellas.us/docs/xospata.pdf. Accessed on October 4, 2024.
50. Lee LY, Hernandez D, Rajkhowa T, Smith SC, Raman JR, Nguyen B, Small D and Levis M: Preclinical studies of gilteritinib, a next-generation FLT3 inhibitor. Blood 129: 257-260, 2017.
51. Mori M, Kaneko N, Ueno Y, Yamada M, Tanaka R, Saito R, Shimada I, Mori K and Kuromitsu S: Gilteritinib, a FLT3/AXL inhibitor, shows antileukemic activity in mouse models of FLT3 mutated acute myeloid leukemia. Invest New Drugs 35: 556-565, 2017.
52. Benmimoun B and Spéder P: Breaking down barriers: Tumors make a leaky brain. Dev Cell 56: 2683-2685, 2021.
53. Slominski RM, Raman C, Chen JY and Slominski AT: How cancer hijacks the body's homeostasis through the neuroendocrine system. Trends Neurosci 46:263-275, 2023.
54. Ruglioni M, Crucitta S, Luculli GI, Tancredi G, Del Giudice ML, Mechelli S, Galimberti S, Danesi R and Del Re M: Understanding mechanisms of resistance to FLT3 inhibitors in adult FLT3-mutated acute myeloid leukemia to guide treatment strategy. Crit Rev Oncol Hematol 201: 104424, 2024.
55. Takahashi S: Downstream molecular pathways of FLT3 in the pathogenesis of acute myeloid leukemia: Biology and therapeutic implications. J Hematol Oncol 4: 13, 2011.
56. Ballesta-López O, Solana-Altabella A, Megías-Vericat JE, Martínez-Cuadrón D and Montesinos P: Gilteritinib use in the treatment of relapsed or refractory acute myeloid leukemia with a FLT3 mutation. Future Oncol 17: 215-227, 2021.
57. Novatcheva ED, Anouty Y, Saunders I, Mangan JK and Goodman AM: FMS-like tyrosine kinase 3 inhibitors for the treatment of acute myeloid leukemia. Clin Lymphoma Myeloma Leuk 22: e161-e184 2022.

58. Wiśniowska B, Tylutki Z, Wyszogrodzka G and Polak S: Drug-drug interactions and QT prolongation as a commonly assessed cardiac effect-comprehensive overview of clinical trials. BMC Pharmacol Toxicol 17: 12, 2016.
59. Kang D, Ludwig E, Jaworowicz D, Huang H, Fiedler-Kelly J, Cortes J, Ganguly S, Khaled S, Krämer A, Levis M, *et al*: Concentration-QTc analysis of quizartinib in patients with relapsed/refractory acute myeloid leukemia. Cancer Chemother Pharmacol 87: 513-523, 2021.
60. Baracaldo-Santamaría D, Llinás-Caballero K, Corso-Ramirez JM, Restrepo CM, Dominguez-Dominguez CA, Fonseca-Mendoza DJ and Calderon-Ospina CA: Genetic and molecular aspects of drug-induced QT interval prolongation. Int J Mol Sci 22: 8090, 2021.
61. Suknuntha K, Choi YJ, Jung HS, Majumder A, Shah S, Slukvin I and Ranheim EA: Megakaryocytic expansion in gilteritinib-treated acute myeloid leukemia patients is associated with AXL inhibition. Front Oncol 10: 585151, 2020.
62. Higgins JPT, Eldridge S and Li T: Chapter 23: Including variants on randomized trials [last updated October 2019]. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ and Welch VA (eds). Cochrane Handbook for Systematic Reviews of Interventions version 6.5. Cochrane, 2024.
63. Higgins JPT, Li T and Deeks JJ (eds): Chapter 6: Choosing effect measures and computing estimates of effect [last updated August 2023]. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ and Welch VA (ed). Cochrane Handbook for Systematic Reviews of Interventions version 6.5. Cochrane, 2024.