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The Impact of Gilteritinib on Overall Survival of Adult Patients with FLT3 Positive Acute Myeloid Leukemia: A Systematic Review

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Abstract

Background: *Gilteritinib, an effective and selective inhibitor of the FLT3 gene, was developed to address the challenges posed by relapsed or refractory acute myeloid leukemia (AML) patients who often encounter limited treatment options and poor prognoses with salvage chemotherapy.*
Aim: *This systematic review aims to explore the progression of interventional research and consolidate existing evidence on the clinical effectiveness of gilteritinib as a monotherapy or combination therapy in improving overall survival among adults experiencing a recurrence or resistance to treatment for FLT3-positive AML patients.*
Methods: *A comprehensive search strategy, utilizing Medical Subject Headings (MeSH) and non-MeSH terms was conducted across Pubmed, EMBASE, Cochrane, and Web of Science databases. We primarily focused on the clinical trial and retrospective studies on gilteritinib as an intervention for relapsed/refractory AML patients.*
Results: *According to our predefined criteria for inclusion and exclusion, we identified 3 published clinical trials and 5 retrospective studies focused on the overall response of gilteritinib on refractory or relapsed AML adult patients published between January 1, 2018, and March 25, 2024. Clinical trial studies demonstrated superior survival outcomes than salvage chemotherapy in the FLT3-positive AML population particularly showing higher efficacy in combination therapy with Azacitidine. Retrospective studies from clinical trials revealed improved clinical outcomes in AML sub-populations.*
Conclusion: *Gilteritinib exhibited promising outcomes by targeting FLT3 receptors, offering a new treatment approach, and revealing improved overall survival compared to salvage chemotherapy in the difficult-to-treat patient population.*

Introduction

Acute Myeloid Leukemia (AML) is a heterogenous malignancy of blood and is characterized by unregulated growth of immature blast cells in both peripheral blood and bone marrow and/or potentially other tissues (Pollyea et al., 2021). Treatments include induction chemotherapy as the first line of therapy, which sometimes involves post-remission or consolidation therapy and maintenance therapy to destroy as many cancer cells as possible. Advances in personalized treatments, focused on sequencing technology, facilitate the molecular profiling of the disease which has led to the development of targeted-based treatment methods. Targeted therapies address specific genetic mutations such as FMS-like tyrosine kinase 3 (FLT3), Isocitrate Dehydrogenase 1 (IDH1), or Isocitrate Dehydrogenase 2 (IDH2) mutations in AML patients. The expected outcomes from targeted therapies are to improve the survival and response rates and reduce the side effects (Totiger et al., 2023).

Nearly 30% of individuals newly diagnosed with acute myeloid leukemia exhibit mutations in the FLT3 gene (Rosnet et al., 1996; Timothy et al., 2013; Welch et al., 2012; Daver et al., 2021; Nakao et al., 1996). These mutations, termed FLT3 activating mutations (FLT3mut), can manifest in two variations: internal tandem duplication mutations (FLT3-ITD) in the juxtamembrane domain (Daver et al., 2021; Nakao et al., 1996) and tyrosine kinase domain mutations (FLT3-TKD) (Daver et al., 2021; Yamamoto et al., 2001; Abu-Duhier et al., 2001). Gilteritinib is a second-generation tyrosine kinase inhibitor (TKI) with potent single-agent activity, effectively targeting both ITD and TKD mutations (Negotei et al., 2023; Lee et al., 2017; Mori et al., 2017; Molica et al., 2023). Tyrosine Kinase Inhibitors are drugs that target specific

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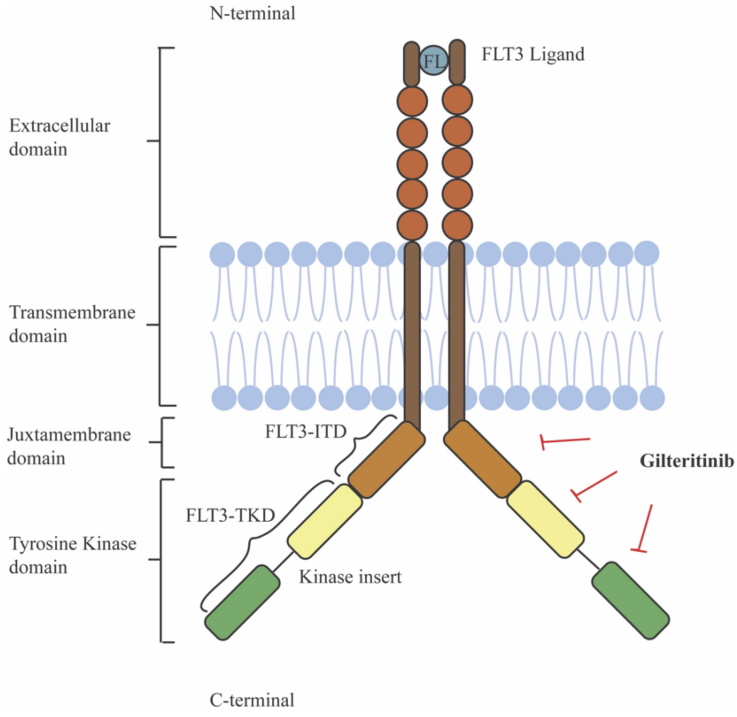

Figure 1: *Gilteritinib mechanism of action on FLT3 receptor.*

enzymes called tyrosine kinases involved in cell signaling and growth regulation of cancer cells (Molica et al., 2023). The structure of the FLT3 receptor with gilteritinib mechanism of action is shown in Figure 1 (Nakao et al., 1996). Among individuals diagnosed with AML, the presence of FLT3-ITD mutations indicates an adverse outcome in terms of overall survival (OS) and relapse-free survival (RFS). FLT3-TKD mutations activate FLT3 making their impact on AML prognosis less linked to adverse outcomes (Rosnet et al., 1996; Timothy et al., 2013; Welch et al., 2012; Daver et al., 2021).

Even among patients with FLT3 mutations, not all meet the criteria of intensive induction due to factors such as advanced age, compromised health status, and underlying co-morbidities, implying the need for alternative treatments. Gilteritinib, a highly specific and potent inhibitor drug, is effective against FLT3 receptors carrying both FLT3-ITD and FLT3-TKD mutations, offering a more tailored therapeutic approach for eligible patients (Lee et al., 2017; Mori et al., 2017). According to the National Comprehensive Cancer Network (NCCN) recommendations (2024), the targeted therapy guidelines included gilteritinib as a category 1 option for AML patients with both FLT3-ITD and FLT3-TKD mutations (NCCN guidelines for AML, 2024 version 2). The objective of this systematic review is to identify and examine existing studies that investigate the outcome of adult AML patients treated with gilteritinib either as a monotherapy or in combination with salvage chemotherapy. This literature research focuses on evaluating and comparing the reported overall survival as a primary outcome, event-free survival, or complete remission as secondary outcomes in different treatment groups to determine the potential effectiveness of gilteritinib.

Materials and Methods

In this systematic review, two PICO questions were addressed. The primary analysis employed the predefined Population, Intervention, Comparison, and Outcome terms to investigate the following research question: Among adult patients with Acute Myeloid Leukemia [P], what is the impact of gilteritinib [I] on overall survival [O] when compared to salvage chemotherapy or combination therapy [C] as a primary line of treatment? In the secondary analysis, the following question was explored: Among adult patients with Acute Myeloid Leukemia [P], what is the impact of gilteritinib [I] on event-free survival and complete remission with full hematological recovery [O] or complete remission with partial hematological recovery [O] when compared to salvage chemotherapy or combination therapy [C] as a primary line of treatment? This review includes literature investigating the advancement of interventional research studies involving gilteritinib as monotherapy or gilteritinib with combination therapies such as post-hematopoietic stem cell transplantation (HSCT) or hypomethylating agents

or salvage chemotherapy to assess their efficacy and survival across diverse patient populations. This research was guided by the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statements where applicable (Liberati et al., 2009). The study characteristics and outcomes tables were subdivided by the methodology of studies with the first category evaluating randomized controlled trials and the second category evaluating observational retrospective studies.

Eligibility Criteria

Clinical trials investigating overall survival, and/or event-free survival, complete-remission, or complete-remission with partial hematological recovery were identified. Inclusion criteria were 1) Clinical trials (randomized or non-randomized, controlled, or non-controlled), observational and retrospective studies. 2) Primary study with gilteritinib as an intervention either as a monotherapy or a combination therapy or with comparator salvage chemotherapy. 3) Studies with adults experiencing refractory or relapsed AML (or harboring positive FLT3 gene mutations). 4) Studies with post-HSCT treatment of patients undergoing gilteritinib treatment. 5) Adult patients (age 18-92) with AML at the time of diagnosis. 6) Patients diagnosed with relapsed or refractory hematological malignancies. 7) Patients who had undergone prior induction chemotherapy or salvage chemotherapy. 8) Studies conducted from 2018 to the present (November 2023). 9) Studies published in English. The most important eligibility criteria were inclusion criteria 1), 2), and 3).

Exclusion criteria were 1) Patients diagnosed with acute promyelocytic leukemia (APL) or chronic myeloid leukemia (CML). 2) Studies on pediatric patients and animals. 3) Studies outside the scope of interest (Overall survival, Event-free survival, complete remission). 4) Studies with patient sample sizes of less than 20. 5) Studies only focused on drug dose escalation, efficacy, and safety. 6) Studies published before 2018. 7) Studies that were case reports, reviews, conference abstracts, and conference publications.

Search Strategy

An initial comprehensive search of articles was conducted on November 23, 2023, with a final follow-up search on March 25, 2024, using a variety of keywords and Mesh terms in Pubmed, Cochrane Library, EMBASE, and Web of Science resulting in the identification of 8 articles. The complete search syntax for PICO is provided below:

1) Acute Myeloid Leukemia OR Acute Myelogenous Leukemia OR Acute Myeloblastic Leukemia OR Acute Granulocytic Leukemia OR Acute Nonlymphoblastic Leukemia OR Acute Nonlymphocytic Leukemia OR Acute Myelocytic Leukemia OR AML OR AGL OR ANLL.
2) Gilteritinib OR Xospata OR ASP2215 OR ASP-2215.
3) 1 and 2.
4) Induction chemotherapy OR Consolidation Chemotherapy OR Maintenance Chemotherapy OR Hematopoietic Stem Cell Transplant OR First-line treatment OR Standard Chemotherapy OR Salvage Chemotherapy.
5) 3 and 4.
6) Survival outcome OR Event-free survival OR Complete remission.
7) 5 and 6.

Data Extraction

Data extraction was conducted independently by one author (SVG) and any discrepancies were resolved in frequent meetings in the presence of the supervisor (BT) which was finally reviewed by the medical expert (NJ). We evaluated Overall Survival (OS), Event-Free Survival (EFS), and Complete Remission (CR) as primary endpoints for analysis. We also assessed Complete Remission with partial hematologic recovery (CRh), Complete Remission with incomplete hematologic recovery (CRi), Complete Remission with incomplete platelet recovery (CRp), and Overall Response Rates (ORR), if available. We compared grade 3 or higher treatment-emergent adverse events (TEAEs) published among these research studies.

Results

Study Selection

The initial search yielded 207 articles, after eliminating 46 duplicates using endnote, 161 articles remained for screening. Further assessment of these articles by conducting a title and abstract review resulted in the exclusion of 102 more articles. Of the 59 remaining articles, 40 were excluded because they were either conference abstracts or the full text was unavailable. 19 potential articles were thoroughly examined, and 11 articles did not meet inclusion criteria, resulting in 8 relevant articles as shown in the Figure 2 PRISMA flow diagram.

Included Studies and Study Characteristics

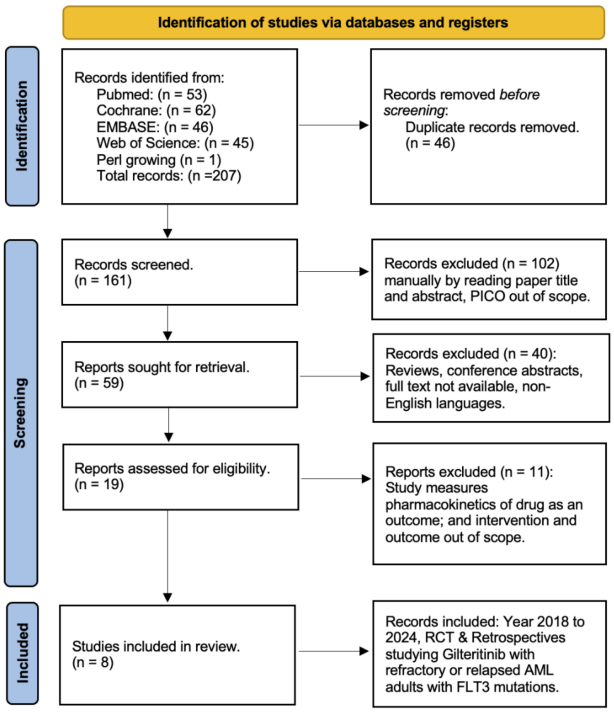

Figure 2: *PRISMA flow diagram.*

Of the 8 studies identified, 3 were randomized controlled trials, and 5 were retrospective observational studies. The 3 randomized clinical trials (Perl et al., 2019), (Wang et al., 2020) and (Levis et al., 2024) were open-label, multicenter, and conducted in 16 different countries. Perl et al. (2019), identified as the ADMIRAL trial, was a large, robust, and diverse population study conducted in 14 countries across Asia, North and South America, and Europe. This study compared the efficacy of gilteritinib treatment with salvage chemotherapy in relapsed or refractory AML patients. Wang et al. (2020), the second RCT, Phase 3 trial, spanned 13 countries across Asia, North and South America, Europe, and Australia, and investigated the potential efficacy of combining gilteritinib with the Azacitidine intervention arm comparing it with Azacitidine as a standalone treatment. The third RCT, (Levis et al., 2024) was another Phase 3 trial, spanning 16 countries across North America, Europe, Asia Pacific, and Rest of World (ROW), that evaluated the effectiveness of gilteritinib post-hematopoietic Cell Transplant maintenance therapy in AML patients harboring an internal tandem duplication mutation of FLT3 (FLT3-ITD) and compared with a placebo arm.

The 5 retrospective studies (Hosono et al., 2021), (Shimony et al., 2022), (Dumas et al., 2023), (Numan et al., 2022) and (Altman et al., 2021) aimed to evaluate the impact of gilteritinib with different comparators on the subpopulation of patients with AML. Various subpopulations included categories relating to patient nationality (n=4), Japanese, French, Israeli, and US. The fifth retrospective study focused on different survival groups after the first line of treatment. Other than the retrospective approach and single population assessment this group of studies differed in their comparator therapies. Hosono et al. (2021) presented a retrospective study specifically targeting the Japanese populations of the ADMIRAL study (Perl et al., 2019) to examine the treatment outcomes and response rate. Shimony et al. (2022), conducted a retrospective study to evaluate gilteritinib as a monotherapy and in combination therapy with hypomethylation agents within the Israeli population. Dumas et al. (2023), a non-interventional, cross-sectional study, examined the gilteritinib activity in relapsed or refractory patients prior treated with intensive chemotherapy and midostaurin within the French population. Numan et al. (2022) studied gilteritinib combined with various high-intensity chemotherapy and compared gilteritinib with hypomethylating agents, gilteritinib with single-agent venetoclax, gilteritinib with other IDH inhibitors within the United States population. The final retrospective study (Altman et al., 2021) evaluated the clearance of FLT3 mutation in relapsed or refractory AML patients following gilteritinib treatment and compared the effectiveness of gilteritinib treatment with conventional chemotherapy regimens. More detailed information

on these studies is provided in Table 1 Study Summary.

Patient and Arm Characteristics

There were 872 intention-to-treat patients in the three RCTs namely Perl et al. (2019), Wang et al. (2022), and Levis et al. (2024). Patients in the gilteritinib arm had a median age of 57.5 and 49% were male; those in the salvage chemotherapy or placebo arm had a median age of 57.3 and 40.9% were male. Wang et al. (2022) had not reported the median age and sex % in their study.

There were 443 patients in the five retrospective studies. These studies included gilteritinib in combination with Salvage chemotherapy, intensive induction, or hypomethylating agents. Patients treated with gilteritinib as a monotherapy or combination therapy in the first arm had a median age of 61 and 44% were male; those in the second arm with gilteritinib in combination therapy had a median age of 63 and 48.3% were male; those in the third arm with gilteritinib as a monotherapy or combination therapy had a median age of 68 and 55% were male. More details are provided in Table 2 Patient and Arm Characteristics.

Study Outcome

The 3 randomized clinical trials evaluated the treatment efficacy of gilteritinib in AML patients with FLT3 mutations. Perl et al. (2019) and Wang et al. (2022) assessed overall survival (OS) and treatment response while Levis et al. (2024) focused on post-hematopoietic stem cell transplant (HCT) maintenance therapy and measurable residual disease detection (MRD) in AML patients with FLT3-ITD mutations. Perl et al. (2019), the ADMIRAL trial, a pivotal multinational phase 3 study evaluated the efficacy of gilteritinib and demonstrated significant prolonged OS and higher rates of remission compared to salvage chemotherapy, highlighting its potential as a therapeutic intervention, improving the quality of life. Additionally, post-HSCT maintenance therapy with gilteritinib showed promising results for patients achieving complete remission or complete remission with partial hematological recovery pretransplant. Their findings collectively highlight the efficacy of gilteritinib in improving the survival outcome and sustained remission in relapsed or refractory acute myeloid leukemia patients with FLT3 mutations. Wang et al. (2022), another multicenter Phase 3 study compared the overall survival (OS), event-free survival (EFS), and response rates among AML patients ineligible for intensive induction chemotherapy (IIC) receiving gilteritinib plus azacitidine (GIL + AZA) in arm 1 and only Azacitidine (AZA) in arm 2. Azacitidine is a hypomethylating agent given as a standalone or as a combination therapy that prevents cancer cells from growing. Despite a longer median follow-up for AZA, GIL + AZA showed numerically longer OS. Median EFS did not significantly differ between the two arms, but sensitivity analysis showed a trend favoring GIL + AZA. In this study, GIL + AZA arms patients respond better in terms of achieving a composite complete response (CRc). Levis et al. (2024) evaluated gilteritinib as HCT and MRD for AML patients with FLT3-ITD mutation and compared it with a placebo arm. OS did not show a statistically significant difference between gilteritinib and placebo (HR, 0.846; P=0.4394). Although the study showed improvement in relapse-free survival (RFS) wasn't statistically significant, overall patients with detectable FLT3-ITD experienced higher RFS rates, indicating the potential efficacy of gilteritinib in this high-risk population who received post-HCT therapy based on MRD detection. The effectiveness of gilteritinib varied geographically demonstrating the highest benefit in North America, limited benefit in Asia/Rest of world, and a slightly adverse effect in Europe. These differences reflect variations in patient population, medical practices, and healthcare systems across these regions.

The 5 retrospective studies (Hosono et al., 2021), (Shimony et al., 2022), (Dumas et al., 2023), (Numan et al., 2022) and (Altman et al., 2021) evaluated the efficacy, and outcome of gilteritinib-treated patients with relapsed or refractory AML harboring FLT3 mutations from existing clinical trial studies in diverse populations including Japanese, Israeli, French, US, Germany, and Italy. Hosono et al. (2021) isolated the Japanese subpopulation from the ADMIRAL trial to evaluate the efficacy of gilteritinib in relapsed or refractory acute myeloid leukemia patients with FLT3 mutations. Their study demonstrated that gilteritinib was well tolerated in the Japanese population and showed superior overall survival (OS), and complete remission (CR) or complete remission with partial hematologic recovery (CRh) than salvage chemotherapy (SC) as shown in the study outcome table. 1-year survival rates in the gilteritinib arm were much higher, 54.3% as compared to 26.3% in the SC arm. Although the results observed in this small specific population study were consistent with the broader ADMIRAL study cohort, there is a need for more robust investigations that aren't dependent on retrospective clinical trial data. Shimony et al. (2022) revealed that gilteritinib significantly showed improved remission rates, superior median OS of 9.6 months, and median

Study Design						Arm 1		Arm 2		Arm 3		Arm 4	
Author, Year	**Type of study**	**Country**	**Study duration**	**Number of patients enrolled #**	**Randomization ratio**	**Intervention**	**Dose**	**Comparator 1**	**Dose**	**Comparator 2**	**Dose**	**Comparator 3**	**Dose**
Perl et al, 2019 (ADMIRAL)	RCT (NCT02421939, Phase 3)	US, Belgium, Canada, France, Germany, Israel, Italy, Japan, Korea, Poland, Spain, Taiwan, Turkey, and UK	October 2015 to February 2018	371	2:01	Gilteritinib	120 mg	Salvage Chemotherapy (SC) (28 Received MEC, 40 Received FLAG-IDA, 16 Received low dose cytarabine, 25 Received azacitidine)	NA	Gilteritinib patients underwent HSCT	NA	SC patients underwent HSCT	NA
Wang et al, 2022	RCT (NCT02752035, Phase 3)	US, Australia, Belgium, Canada, France, Germany Italy, Japan, Republic of Korea, Poland, Spain, Taiwan, and UK	December 2017 to August 2020	145	1:01:01	Gilteritinib + Azacitidine	80 to 120 mg	Azacitidine	75 mg	Gilteritinib	NA	NA	NA
Levis et al, 2024	RCT (NCT02997202, Phase 3)	US, Australia, Belgium, Canada, Denmark, France, Germany, Greece, Italy, Japan, Republic of Korea, New Zealand, Poland, Spain, Taiwan, UK	June 2017 to July 2023	356	NA	Gilteritinib	120mg	Placebo	NA	NA	NA	NA	NA
Hosono et al, 2021	Retrospective (NCT02421939, Phase 3)	Japan	October 2015 to February 2018	48	2:01	Gilteritinib	120 mg	Salvage Chemotherapy (2 Received MEC, 1 Received FLAG-IDA, 8 Received low dose cytarabine, 3 Received azacitidine)	NA	NA	NA	NA	NA
Shimony et al, 2022	Retrospective analysis, Multicenter	Israel	January 2019 to September 2021	20	1:01	Gilteritinib + overall cohort	120 mg	Gilteritinib + intensive induction	120 mg	Gilteritinib + HMA-Venetoclax	NA	NA	NA
Dumas et al, 2023	Non-interventional ambispective cross-sectional study (NCT05193448)	France	March 2019 to March 2021	167	NA	Cohort A - Gilteritinib + combination of chemotherapy drugs (includes patient with FLT3-ITD and/or TKD mutated AML)	NA	Cohort B - Gilteritinib as a single agent (where 50% patients received midostaurin and rest 50% didn't received midostaurin)	NA	Cohort C - Gilteritinib with prior exposure to "3 + 7 + midostaurin"	NA	NA	NA
Numan et al, 2022	Retrospective, multicenter study	US	January 2020 to June 2021	113	NA	Gilteritinib combined with high intensity chemotherapy (FLAG, CPX-351, CLIA, CLAG, MEC)	NA	Gilteritinib with Hypomethylating agents (Decitabine or Azacitidine)	NA	Gilteritinib with single-agent Venetoclax or Venetoclax with HMA	NA	Gilteritinib combined with IDH inhibitor	NA
Altman et al, 2021	Retrospective, multicenter study (NCT02014558, Phase 1 and 2)	United States, Germany, and Italy	October 2013 to August 2015	95	NA	Gilteritinib + FLT3-ITD (cleared)	>= 80 mg	Gilteritinib + FLT3-ITD (Not cleared)	>=80 mg	Combined	>=80 mg	NA	NA

Abbreviations: RCT, Randomized Clinical trial; FLT3-ITD, Fumase-Like Tyrosine Kinase 3-Internal Tandem Duplication; TKD, Tyrosine Kinase Domain; FLAG, (Fludarabine, Arabinofuranosyl cytidine Granulocyte colony-stimulating factor); CPX-351, (daunorubicin and cytarabine); CLIA, (Cladribine, idarubicin, and cytarabine); CLAG, (Cladribine, Cytarabine, and Filgrastim); MEC, (Mitoxantrone, Etoposide and Cytarabine); FLAG-IDA, (Fludarabine cytarabine iDArubicin and filgrastim); HSCT, Hematopoietic Stem Cell Transplant; IDH, Isocitrate Dehydrogenase.

Table 1: *Study summary.*

EFS of 5.1 months than 7 months of OS and 3.3 months of EFS in standard of care (SOC) salvage therapy in Israeli patients pre-treated with Tyrosine Kinase Inhibitors (TKIs). Dumas et al. (2023) conducted a non-interventional ambispective study in the French population. They showed promising activity of gilteritinib in patients with refractory or relapsed FLT3 mutated AML after prior intensive chemotherapy and midostaurin, a first-generation FLT3 inhibitor (TKI) (Perl et al., 2022). These findings indicate the promising therapeutic potential of gilteritinib, a second-generation FLT3 inhibitor effective against both FLT3-ITD and TKD mutations (Perl et al., 2019), as a viable treatment alternative for relapsed or refractory FLT3 mutated AML patients after undergoing intensive treatment regimens. Numan et al. (2022) conducted a retrospective study in the US population and focused on evaluating the clinical activity of gilteritinib in clearing mutations in patients with refractory or relapsed FLT3 mutated AML who had been previously treated with FLT3 inhibitors such as midostaurin and sorafenib. The median OS was 7.0 months in the gilteritinib arm and 48.7% achieved CRc, 22.1% achieved CR and 26.7% achieved CRi or CRp which was comparable to 53.9% in midostaurin, and 41.2% in sorafenib. Gilteritinib in combination therapy achieved higher CRc rates (64%) as compared to single-agent use (43%) but no survival advantage of combination therapy over single-agent was proved. Their further findings assessed the ability of gilteritinib to target and clear FLT3 mutations which are associated with poor prognosis in AML. Their study suggested a favorable mutation clearance with gilteritinib treatment. Altman et al. (2021) conducted a retrospective study, across the US, Germany, and Italy populations. They investigated the effect of FLT3 mutation clearance, treatment response post-gilteritinib therapy, and overall survival in patients with refractory or relapsed FLT3 mutated AML. Their study provided insights into the potential benefits of achieving FLT3 mutation clearance and favorable treatment response contributing to improved overall survival outcomes in this challenging patient population. These studies collectively demonstrate gilteritinib as an effective treatment option for relapsed or refractory FLT3 mutated AML patients who have previously undergone intensive treatments such as chemotherapy, hypomethylating agents, or tyrosine kinase inhibitors. These studies revealed improved survival outcomes and achieved favorable treatment responses including mutation clearance and overall survival improvement. More details can be found in Table 3 Study Outcome. The Study outcome table covers only 6 of the 8 studies because of the incomplete data provided by the remaining 2 studies (Levis et al., 2024; Altman et al., 2021).

Adverse Effects

The 3 RCTs, Perl et al. (2019), Wang et al. (2022), and Levis et al. (2024) reported both hematological and non-hematological adverse events with gilteritinib treatment in FLT3 mutated AML patients. Perl et al. (2019), the ADMIRAL trial, reported several adverse effects during its course. Notable serious adverse events of grade 3 include febrile neutropenia (45.9%), anemia (40.7 %), and aminotransferase increase (>13%). Discontinuation of gilteritinib was due to elevated liver enzymes, pneumonia, large intestine perforation, and septic shock. The study also recorded a substantial number of deaths in the chemotherapy group (74.3%) than in the gilteritinib group (69.1%). These findings emphasize the importance of monitoring and managing adverse effects during gilteritinib treatment in this patient population. Wang et al. (2022) reported higher adverse effects which were 100% from the combination therapy of gilteritinib with Azacitidine (GIL + AZA) in comparison to Azacitidine monotherapy which was 95.7%. The combination group reported more grade >3 adverse events (95.9%) and a higher proportion of related deaths than the AZA group (89.4%). Their findings highlight the increased risk of certain adverse effects associated with combination therapy compared to AZA monotherapy in AML patients. Levis et al. (2024) study showed higher rates of (grade 3 or more) treatment-emergent adverse events (TEAEs) particularly myelosuppression and infection which led to withdrawals from gilteritinib treatment. Despite the lack of significant improvement in RFS, the early initiation of low doses of gilteritinib maintenance therapy may still offer some prognostic benefits.

In 2 retrospective studies, Hosono et al. (2021) and Dumas et al. (2021) observed serious TEAEs during gilteritinib therapy leading to discontinuation due to adverse event rates in both studies. Hosono et al. (2021) reported higher rates of TEAEs with gilteritinib (100%) compared to standard chemotherapy (93%). Drug-related adverse events were more common with gilteritinib (88%) than salvage chemotherapy (77%) leading to discontinuation in some cases. Despite longer exposure, gilteritinib had a lower incidence of TEAEs than salvage chemotherapy. Despite differences in demographics and other factors, this study reported that there were no unique clinically significant TEAEs observed in Japanese patients compared to the overall cohort. Dumas et al. (2021) reported 28.3% of patients

observed serious adverse events during treatment including infections (56.4%), hemorrhage (2.6%), cardiovascular issues (10.3%), and differentiation syndrome (5.2%). Gilteritinib treatment was discontinued in 66.9% of the patient population primarily due to lack of efficacy or hematological toxicity and other adverse events. Shimony et al. (2022), Numan et al. (2022), and Altman et al. (2021) did not discuss any hematological and non-hematological adverse events relevant to our study. Despite several variations in adverse events and treatment strategies, these studies underscore the importance of monitoring and managing adverse effects during the gilteritinib treatment in FLT3-positive AML patients, particularly noting higher rates of adverse events occurring with combination therapy compared to monotherapy. Hematological and non-hematological adverse events were addressed in 5 of the 8 studies as presented in the Adverse Events Table 4. For a more detailed understanding of adverse events, see Supplementary Table 1.

Risk of Bias

The risk of bias and quality of studies was assessed for randomized controlled studies using the Cochrane ROB 2 tool (Higgins et al., 2011). All three RCTs (Perl et al., 2019; Wang et al., 2022; Levis et al., 2024) presented a low risk for selection bias: random sequence generation, allocation concealment, and low risk for incomplete assessment and selective reporting bias. Two RCTs (Perl et al., 2019; Wang et al., 2022) had some concerns about blinding participants and blinding outcome assessment. The risk of Bias was evaluated for the five retrospective studies (Numan et al., 2022; Hosono et al., 2021; Dumas et al., 2023; Shimony et al., 2022; Altman et al., 2021) by following the ROBINS-I tool (Sterne et al., 2016). All the retrospective studies posed some concerns and risks due to confounding, selection of patients into the study, and measurement outcome as the criteria for isolating the subpopulation were not transparent, leading to biased estimates of treatment effects. The bias in the classification of interventions, bias due to missing data, and selection of reported results were presented as high-risk factors. This assessment stems from a lack of clear rationale for isolating the subpopulation, and the completeness of data collection cannot be assessed completely. There is a weakness in reporting these studies as they all had different comparators or a combination of comparators.

Discussion

This systematic review combined the data from 3 randomized controlled trials (Perl et al., 2019), (Wang et al., 2020) and (Levis et al., 2024) and 5 retrospective studies (Hosono et al., 2021), (Shimony et al., 2022), (Dumas et al., 2023), (Numan et al., 2022) and (Altman et al., 2021) analyzing subpopulations from various countries and trials on gilteritinib efficacy and survival outcomes of AML patients with FLT3 mutations. Despite methodological differences in findings from both RCTs and retrospective studies consistently demonstrated gilteritinib efficacy in improving the survival outcome in this high-risk patient population as compared to various comparators (see Table 3. Study Outcome). The ADMIRAL trial highlighted significant improvements in overall survival and remission rates compared to salvage chemotherapy, emphasizing its potential to enhance patient outcomes and quality of life. Furthermore, in Wang et al. (2022) study, the effectiveness of combining gilteritinib in combination with azacitidine was examined and compared to azacitidine as monotherapy. The results revealed significant improvements with the combination therapy, including a 67% increase in overall survival and a 30% enhancement in response rates compared to AZA as a standalone treatment. Retrospective subpopulation studies such as Hosono's study on the Japanese population, although in a smaller cohort, supported the efficacy of gilteritinib in improving overall survival and remission rates compared to salvage chemotherapy.

Similarly, studies across different populations, such as Shimony et al. (2022) study in Israeli patients and Dumas et al. (2023) study in the French population, indicated a promising activity of gilteritinib in patients with refractory or relapsed FLT3 mutated AML. The inclusion of subpopulation analysis from different countries enhances the generalizability of the findings, suggesting that gilteritinib may be effective across diverse patient populations. There was a notable preponderance of male patients treated with gilteritinib, particularly around the age of 60 years from these diverse populations. While RCTs provide robust evidence and methodological variations, retrospective studies offer insights into real-world effectiveness. The combined strengths and evidence of both methodologies support the use of gilteritinib in managing AML with FLT3 mutations, particularly in the subpopulations analyzed in retrospective studies. Limitations such as retrospective study biases and the potential for unmeasured confounders such as previous treatments, genetic variations in the population of study, co-morbidities may affect the interpretation of the results. Additionally, heterogeneity across RCTs and retrospective studies could influence the pooled estimates. This heterogeneity refers to the variability in the study design, different populations, gilteritinib with combination therapy as intervention,

		Arm 1				Arm 2					Arm 3				Arm 4				
Author, Year	**Intervention**	**Dose**	**Number of patients**	**Median Age**	**Sex (Male%)**	**Comparator 1**	**Dose**	**Number of patients**	**Median Age**	**Sex (Male%)**	**Comparator 2**	**Dose**	**Number of patients**	**Median Age**	**Sex (Male%)**	**Comparator 3**	**Dose**	**Number of patients**	**Median Age**	**Sex (Male%)**
Perl et al, 2019 (ADMIRAL Trial)	Gilteritinib	120 mg	246	62	47	Salvage Chemotherapy (28 Received MEC, 40 Received FLAG-IDA, 16 Received low dose cytarabine, 25 Received azacitidine)	NA	109	61.5	30	Gilteritinib patients arm underwent HSCT	NA	63	NA	NA	Salvage Chemotherapy patients arm underwent HSCT	NA	19	NA	NA
Wang et al, 2022	Gilteritinib + Azacitidine	80 to 120 mg	73	NA	NA	Azacitidine	75 mg	49	NA	NA	Gilteritinib	NA	22	NA	NA	–	–	–	–	–
Levis et al, 2024	Gilteritinib	120 mg	178	53	51.1	Placebo	NA	177	53	51.7	–	–	–	–	–	–	–	–	–	–
Hosono et al, 2021	Gilteritinib	120 mg	33	60	42	Salvage Chemotherapy (2 Received MEC, 1 Received FLAG-IDA, 8 Received low dose cytarabine, 3 Received azacitidine)	NA	14	69	40	–	–	–	–	–	–	–	–	–	–
Shimony et al, 2022	Gilteritinib + overall cohort	120 mg	20	61	52	Gilteritinib + intensive induction	120 mg	15	59	50	Gilteritinib + HMA-Venetoclax	NA	5	80	60	–	–	–	–	–
Dumas et al, 2023	Cohort A - Gilteritinib + combination of chemotherapy drugs (includes patient with FLT3-ITD and/or TKD mutated AML)	NA	167 (Gil as a single agent = 140, combination = 27)	63.4	52.7	Cohort B - Gilteritinib as a single agent (50% patients received mido and rest 50% didn't received mido)	NA	140	63.9	54.3	Cohort C - Gilteritinib with prior exposure to "3 + 7 + mido"	NA	67	62.5	56.7	–	–	–	–	–
Numan et al, 2022	Gilteritinib combination with high intensity chemotherapy (FLAG, CPX-351, CLIA, CLAG, MEC)	13 mg	NA	NA	NA	Gilteritinib with Hypomethylating agents (Decitabine or Azacitidine)	NA	14	NA	NA	Gilteritinib with single-agent Venetoclax or Venetoclax with HMA	NA	13	NA	NA	Gilteritinib combined with IDH inhibitor	NA	2	NA	NA
Altman et al, 2021	Gilteritinib + FLT3-ITD (cleared)	>= 80 mg	10	59.5	30	Gilteritinib + FLT3-ITD (Not cleared)	>= 80 mg	85	61	49	Combined	>= 80 mg	95	61	48	–	–	–	–	–

Table 2: *Patient and arm characteristics.*

	Perl (2019)		**Wang (2022)**		**Hosono (2021)**		**Shimony (2022)**		**Dumas (2023)**			**Numan (2022)**		
Variable	**Gil. (N=247)**	**SC (N=124)**	**Gil + Aza (n=74)**	**Aza (n=49)**	**Gil. (N=33)**	**SC (N=15)**	**Gil. (n=9)**	**Standard Of Care (SOC) (n=9)**	**Cohort A Overall Study (n=167) Single agent (n=140), combination (n=27)**	**Cohort B Single agent Gil. (n=140)**	**Cohort C Gil. with prior exposure to "3+7+mido" (n=67)**	**Gil. post treatment with other agents**	**Midostaurin**	**Sorafenib**
Median Overall Survival (OS) (95% CI) — months	9.3 (7.7-10.7)	5.6 (4.7-7.3)	16.7	10	14.3	9.6	9.6	7	6.4	6.4	7.8	7	7.8	5
Median Event-Free Survival (95% CI) — months	2.8 (1.4–3.7)	0.7 (0.2–NE)	0.03	0.03			5.1	3.3		3.9	3.9			
response — number (%)			47 (63.5)	17 (34.7)										
Complete Remission (CR)	52 (21.1)	13 (10.5)	12 (6.2)	7 (14.3)	8 (24.2)	1 (6.7)			24 (15.4)	22 (16.9)	12 (19.4)	22.1 (25)		
Complete remission or Complete remission with partial hematologic recovery (CR/ CRh)	84 (34.0)	19 (15.3)	19 (25.7)	8 (16.3)	16 (48.5)	2 (13.3)								
Complete Remission with partial hematologic recovery (CRh)	32 (13.0)	6 (4.8)	7 (9.5)	1 (2.0)	8 (24.2)	1 (6.7)								
Complete Remission with incomplete hematologic recovery (CRi)	63 (25.5)	14 (11.3)	25 (33.8)	6 (12.2)	8 (24.2)	2 (13.3)			14 (9.0)	8 (6.2)	4 (6.5)			
Complete Remission with incomplete platelet recovery (CRp)	19 (7.7)	0	6 (8.1)	0	3 (9.1)	0			3 (1.9)	3 (2.3)	1 (1.6)	30 (26.5)		
Partial remission (pr)	33 (13.4)	5 (4.0)	4 (5.4)	4 (8.2)	5 (15.2)	1 (6.7)			10 (6.4)	7 (5.4)	4 (6.5)			
No Response (NR)	66 (26.7)	43 (34.7)	10 (13.5)	17 (34.7)	9 (27.3)	5 (33.3)								
Composite Complete Remission (CRc)	134 (54.3)	27 (21.8)	43 (58.1)	13 (26.5)	19 (57.6)	3 (20.0)			41 (26.3)	33 (25.4)	17 (27.5)	55 (48.7)	53.9	41.2
Overall Response Rate (ORR)	167 (67.6)	32 (25.8)			24 (72.7)	4 (26.7)			51 (32.7)	40 (30.8)	21 (34)			
Median duration of remission (95% CI) — months	11.0 (4.6–NE)	NE (NE–NE)												
Time to composite complete remission — months	2.3±1.9	1.3±0.5												
Median leukemia-free survival (95% CI) — months	4.4 (3.6–5.2	6.7 (2.1–8.5)												
Not evaluable (NE)			2 (2.7)	1 (2.0)	0	6 (40.0)								

Number of patients (percent); abbreviations: NE, Not Evaluable; Gil, Gilteritinib; Aza, Azacitidine.

Table 3: *Study outcome.*

		Perl (2019)		Wang (2022)		Levis (2024)		Hosono (2021)				Dumas (2023)		
Adverse Events		**Arm 1 Gilteritinib (n=246)**	**(Arm 2) Salvage Chemotherapy (n=109)**	**(Arm 1) Gilteritinib + Azacitidine (n=73)**	**(Arm 2) Azacitidine (n=47)**	**(Arm 1) Gilteritinib (n=178)**	**(Arm 2) Placebo (n=177)**	**(Arm 1) Gilteritinib in Japanese patients (n=33)**	**(Arm 1) Gilteritinib in all other patients (n=213)**	**(Arm 2) Salvage Chemotherapy in Japanese patients (n=14)**	**(Arm 2) Salvage Chemotherapy in all other patients (n=95)**	**(Arm 1) Overall study n=167 (100%) Single agent n= 140 combo n=27**	**(Arm 2) Single agent gilteritinib n=140 (100%) No prior mido n=70 Prior mido n=70**	**(Arm 3) Single agent gilteritinib & prior exposure to "3 + 7 + mido" n=67 (100%)**
Hematological	**Febrile Neutropenia**	113 (45.9)	40 (36.7)	26 (35.6)	9 (19.1)	NA	NA	12 (36)	26 (12)	3 (21)	17 (18)	NA	NA	NA
	Platelet count decreased	54 (22)	27 (24.8)	13 (17.8)	9 (19.1)	38 (21.3)	20 (11.3)	9 (27)	21 (10)	4 (29)	10 (11)	NA	NA	NA
	Anemia	100 (40.7)	33 (30.3)	18 (24.7)	13 (27.7)	17 (9.6)	14 (7.9)	8 (24)	40 (19)	6 (43)	15 (16)	68 (41)	56 (40.3)	24 (35.8)
	WBC count decreased	NA	NA	NA	NA	18 (10.1)	3 (1.7)	6 (18)	20 (9)	4 (29)	10 (11)	NA	NA	NA
Non-hematologic	**Alanine aminotransferase increased**	34 (13.8)	5 (4.6)	NA	NA	11 (6.2)	8 (4.5)	6 (18)	13 (6)	0	2 (2)	NA	NA	NA
	Aspartate aminotransferase increased	36 (14.6)	2 (1.8)	4 (5.5)	0	11 (6.2)	6 (3.4)	6 (18)	14 (7)	0	1 (1)	NA	NA	NA
	Pyrexia	8 (3.3)	4 (3.7)	7 (9.6)	0	NA	NA	NA	NA	NA	NA	NA	NA	NA

Number of patients (percent)
Abbreviations: Mido, Midostaurin; Combo, Combination therapy.

Table 4: *Adverse events.*

Tool	Study	Selection bias: Random Sequence Generation	Selection bias: Allocation concealment	Performance bias: Blinding of participants	Detection bias: Blinding outcome assessment	Attrition bias: Incomplete outcome assessment	Selective reporting
ROB 2 Tool	Perl et al., (2019)	🟢	🟢	🟡	🟡	🟢	🟢
	Wang et al., (2022)	🟢	🟢	🟡	🟡	🟢	🟢
	Levis et al., (2024)	🟢	🟢	🟢	🟢	🟢	🟢
	Study	**Bias due to confounding**	**Bias due to selection of patients into the study**	**Bias in Classification of interventions**	**Bias due to missing data**	**Bias in measurement outcomes**	**Bias in selection of reported result**
ROBINS-1 Tool	Numan et al., (2022)	🟡	🟡	🔴	🔴	🟡	🔴
	Hosono et al., (2021)	🟡	🟡	🔴	🔴	🟡	🔴
	Dumas et al., (2023)	🟡	🟡	🔴	🔴	🟡	🔴
	Shimony et al., (2022)	🟡	🟡	🔴	🔴	🟡	🔴
	Altman et al., (2021)	🟡	🟡	🔴	🔴	🟡	🔴

Low risk 🟢
High risk 🔴
Some concerns 🟡

Table 5: *Risk of bias assessment.*

outcomes measured and methodologies.

Conclusion

This review highlights a critical research gap emphasizing the necessity for additional clinical trials on the efficacy of gilteritinib in treating relapsed and refractory FLT3-positive patients with AML. Clinical practice guidelines (NCCN guidelines for AML, 2024 version 2) and clinical trials such as the ADMIRAL trial (Perl et al., 2019), recommend gilteritinib in clinical practice due to its demonstrated efficacy in improving overall survival and event-free survival compared to standard chemotherapy. The information we present regarding gilteritinib use in patients can significantly impact clinical decisions, aid in the timely and appropriate use based on disease staging and severity. Future studies should focus on conducting robust prospective studies to confirm the observed benefits of gilteritinib across diverse patient subpopulations, disease staging, and clinical settings. Further patient profiling is needed to understand how patients would respond to gilteritinib treatment as a first-line or second-line treatment, needs to be explored in future randomized clinical trials. In cases of later-stage detection, gilteritinib could provide an effective initial treatment option. While considering alternative first-line treatments, other second-generation FLT3 inhibitors such as quizartinib could be evaluated for comparison with gilteritinib. A head-to-head study comparing the efficacy and safety of gilteritinib with quizartinib, both second-generation FLT3 inhibitors, would be beneficial for assessing their relative benefits and risks in treating FLT3-positive AML patients.

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Supplementary Materials

Supplementary Table 1: Adverse Effect

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Conflicts of Interest

The authors declare no conflict of interest.

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