Article published online: 2025-07-10

Gilteritinib

Harini Raghunathan[1] Parathan Karunakaran[1]

[1] Department of Medical Oncology, Cancer Institute (WIA), Chennai, Tamil Nadu, India

Address for correspondence Parathan Karunakaran, MD, DM, Cancer Institute (WIA), 38, Sardar Patel Road, Chennai 600 036, Tamil Nadu, India (e-mail: drparathan@gmail.com).

Ind J Med Paediatr Oncol 2025;46:600–604.

Abstract

Introduction Acute myeloid leukemia (AML) is a heterogeneous and aggressive form of blood cancer that affects the myeloid lineage of the cells. Among various genetic mutations associated with AML, the *FLT-3* mutation is one of the most common and associated with poor prognosis. Gilteritinib (previously known as ASP2215) is the first tyrosine kinase inhibitor approved as monotherapy for treatment of relapsed/refractory AML.

Areas Covered We review gilteritinib in detail, including its mechanism of action, pharmacology, efficacy, toxicity profile, and key clinical trials.

Keywords
- FLT3 mutation
- relapsed/refractory AML
- TKI
- gilteritinib

Introduction

Acute myeloid leukemia (AML) has an annual incidence of approximately 2 to 3 per 100,000 in adults in India. Fms-related tyrosine kinase 3 (*FLT3*) gene, which encodes type III receptor tyrosine kinase protein, is the most common gene that is mutated in AML.

FLT3-mutated AML is characterized by a younger age of onset, high white blood cell count, and high blast percentage at presentation, along with an elevated lactate dehydrogenase. It does achieve remission with conventional therapy, but has a pronounced tendency to relapse, relapse quickly, and die sooner.

Based on the interim results of the ADMIRAL study, gilteritinib was approved by the U.S. Food and Drug Administration (FDA) in November 2018 for the treatment of adults with relapsed and/or refractory (R/R) AML with a *FLT3* mutation.[1] It has been available in India since April 2024. ►**Table 1** summarizes the drugs available with *FLT3* activity.

Gilteritinib

Mechanism of Action

Gilteritinib is a highly selective FLT3 inhibitor, which has activity against both *FLT3-ITD* and *FLT-TKD* mutations. In comparison, midostaurin has slightly lower efficacy against *FLT3-TKD*. Gilteritinib also inhibits *ALK* and *AXL*, which is overexpressed in AML and has shown potential role in chemoresistance.[2]

Pharmacokinetics

Maximum plasma concentration achieved: 4 to 6 hours. High-fat meal delays it by 2 hours.

It is metabolized via CYP3A4, and it is excreted mainly via feces. It has a long elimination half-life of 113 hours, permitting once daily dosing.[2]

Drug Interactions

Strong CYP3A inhibitors (voriconazole, posaconazole) increase gilteritinib levels by 34.24%. Hence, dose reduction to 80 mg is advised. However, effect on efficacy is not known. It is pertinent to note that the ADMIRAL trial did not utilize these azoles for prophylaxis.[3]

Safety[1,4]

Gilteritinib is generally well-tolerated compared with traditional chemotherapy. Its nonhematological toxicity includes:

1. Aspartate and alanine aminotransferase elevation was the most commonly reported adverse effect (AE).

article published online
July 10, 2025

DOI https://doi.org/10.1055/s-0045-1809991.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Table 1 FDA-approved drugs for *FLT3*-mutated AML

Drug	Type	*FLT3* activity	Generation	Selectivity	Upfront therapy	Relapsed therapy
Sorafenib	2	Only ITD	1	Multikinase inhibitor (*FLT3, VEGFR, PDGFR*)		
Midostaurin	1	ITD and TKD	1	Multikinase inhibitor	As combination	
Quizartinib	2	Only ITD	2	*FLT3*	As combination	
Gilteritinib	1	ITD and TKD	2	*FLT3*, *ALK*, *AXL*		Monotherapy

Abbreviations: AML, acute myeloid leukemia; FDA, Food and Drug Administration; ITD, internal tandem duplication; TKD, tyrosine kinase domain.

2. QT segment prolongation
   Recommendation is for electrocardiogram monitoring on days 1, 8, and 15 of cycle 1 and day 1 of subsequent cycles. It is advised to withhold the drug if QTc > 500 ms, and restart at a lower dose once the QTc < 480 ms. Periodic potassium and magnesium monitoring is mandated.
3. Differentiation syndrome (DS)[5]
   DS is a unique side effect initially reported with the use of all-trans retinoic acid in acute promyelocytic leukemia (APML). In the therapy of AML, gilteritinib shares this unique AE with the isocitrate dehydrogenase (IDH) inhibitors. Unlike DS seen in APML, DS occurs less frequently, has a later onset, and is associated with prominent skin involvement, in the form of Sweet's syndrome.
4. Gastrointestinal (GI) disturbances, muscle pain, fatigue, dizziness, and peripheral edema have also been reported.
5. Rare but serious toxicities include posterior reversible encephalopathy syndrome and Pancreatitis.

Clinical Efficacy

Approval for gilteritinib was obtained based on the results of CHRYSALIS and ADMIRAL trials.

CHRYSALIS Trial[5]

This is the first-in-human, open-label, phase I/II dose escalation, dose expansion trial in R/R AML.

Dose ranged from 20 to 450 mg, with maximum tolerated dose identified as 300 mg.

ADMIRAL Trial[1]

This global, open-label, phase III trial enrolled 371 adult patients with R/R *FLT3*-mutated AML. Assigned 2:1 to either gilteritinib or salvage chemotherapy (MEC/FLAG-Ida/azacitidine [Aza]/low dose cytarabine). The median overall survival was 9.3 months in the gilteritinib group compared with 5.6 months in the chemo group. The objective response rate was considerably higher in the gilteritinib group (67.6% vs. 25.8%). Similarly, gilteritinib demonstrated a longer duration of response (11 vs. 1.8 months).

MORPHO Trial[6]

This phase 3 trial by the BMT CTN group evaluated gilteritinib as maintenance therapy posttransplant. The strongest benefit was seen in patients who were MRD (measurable residual disease) positive in the peritransplant period, whereas no benefit was observed in patients who were MRD-negative.

The posttransplant relapse kinetics demonstrated that those who did not receive maintenance relapsed early (64.3% relapsed within 8 weeks and 93.9% by 16 weeks). Whereas clonal eradication due to graft versus leukemia occurred only by 3 to 6 months. Based on these kinetics in MRD-positive cases, it is advised that gilteritinib should be started soon after engraftment.

Current Uses

As Monotherapy

It is the only *FLT3* inhibitor approved as monotherapy by the FDA in the relapsed setting.

As Combination Therapy

Combination therapy is preferred in the front-line setting. The Lacewing study initially included a monotherapy arm upfront, however, it was dropped midway through the trial, due to changing treatment paradigm. ►**Table 2** summarizes the trials with gilteritinib combination therapy.

1. Gilteritinib with venetoclax[7]
   It is hypothesized that targeting both *FLT3* and *BCL-2* pathways may enhance cell death in *FLT3*-mutated AML cells. Pharmacological modeling also suggests higher synergism between gilteritinib and venetoclax in comparison to midostaurin.[8]
2. Gilteritinib with Aza[9]
   Aza is believed to enhance *FLT3* inhibition by reducing cellular proliferation. The combination has shown manageable toxicity in elderly AML. However, the Lacewing study failed to demonstrate survival benefit for the addition of gilteritinib to Aza.[9] GI toxicity, especially, GI hemorrhage, was higher with gilteritinib + Aza.
3. Triple therapy: Gilteritinib with Aza and venetoclax[10]
   It is the preferred combination and has proven to have the best efficacy. However, it is associated with higher toxicity with a 62% incidence of infection and 38% febrile neutropenia, More so with R/R AML.
4. Gilteritinib and chemotherapy[3,11]
   Adding gilteritinib to standard chemotherapeutic regimens can induce a deeper molecular response by targeting residual disease more effectively than chemotherapy. However, concern exists regarding the efficacy of gilteritinib in this setting, as there is rebound increase in wild-type *FLT3*, induced by the recovering marrow post-chemotherapy.

Table 2 Trials of combination therapy with gilteritinib

Trial / Phase	*n*	Patient profile	ORR	CR	OS	PFS	Key message
Venetoclax plus gilteritinib[7] phase IB	61	Failed > 1 line of AML therapy	-	mCRc- 75%[a]	10 months	–	Ven + Gilt had high mCRc, regardless of prior FLT3 inhibitor exposure
Triple therapy with venetoclax, FLT3 inhibitor, and decitabine for FLT3-mutated AML[9]– Phase II trial	25	Newly diagnosed AML and R/R AML Excl. favorable cytogenetics and prior venetoclax exposure	Newly diagnosed 67–92% R/R AML 26–83%	Newly diagnosed CRc- 92% R/R AML CRc- 62%	Newly diagnosed OS not reached (2-year OS – 80%) R/R AML 6.8 months	Newly diagnosed 18-month PFS-59% R/R AML- 58%	Triplet therapy safe and effective
Lacewing trial[10] Phase III trial	123	Newly diagnosed AML patients ineligible for intensive chemotherapy		Gilt + AZA- CRc- 58% CR- 16.2% AZA CRc–26.5% CR-14.3%	Gilt + AZA -9.8 months AZA- 8.8 months	EFS Gilt + AZA- 4.5 months AZA-0.3 months	Negative study
Gilteritinib + 3 + 7 chemotherapy[3] phase I B trial	80	Newly diagnosed, fit for intensive chemotherapy Gilt in induction, consolidation, and maintenance	–	FLT-3 WT -CRc- 50% FLT3–mutated CRc-89%	mOS- 46.1 months	–	Gilteritinib can be safely combined with conventional 3 + 7 therapy. It induced prolonged myelosuppression. Gilteritinib maintenance well tolerated
Gilt plus CLIA chemotherapy (cladribine, idarubicin, cytarabine) ± venetoclax[11] Phase II trial	18	Newly diagnosed, fit for intensive chemotherapy	CLIA + gilteritinib 80% Vs. CLIA+ gilteritinib + venetoclax 88%		21. 9 months For entire cohort (not reached for CLIA + Gil arm and 22.4 months in CLIA + Gil + Ven arm		Addition of venetoclax produced similar results but prolonged the count recovery

Abbreviations: Aza, Azacitidine; AML, acute myeloid leukemia; CRh, complete remission; Cri, complete remission with incomplete hematological recovery; CRc, composite CR (CR + Cri + CRh); Gilt, Gilteritinib; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed and/or refractory; Ven, Venetoclax.

Use of Gilteritinib Post-Failure of Other FLT3i[12]

There is a concern that prior use of FLT3i can drive the expansion of clones with additional on-target mutations, which may confer resistance to gilteritinib. However, data from the Admiral trial and real-world data clearly demonstrated its efficacy in this population (composite complete remission [CR] rates of ~50%).

Maintenance Therapy for Nontransplant patients[13]

Gilteritinib maintenance is more effective in preventing early relapse at 0.5 to 1 year. However, its utility is limited if the MRD is negative.

Myeloid Sarcoma[14]

Shatilova et al have reported superior efficacy of gilteritinib over other *FLT3*i for the therapy of extramedullary disease.

Dosing[1,7,9–11]

The dose of gilteritinib is 120 mg for monotherapy (only FDA-approved dose).

Dose escalation up to 200 mg was permitted if the patient is not in CR at 28 days of treatment.

Gilteritinib is used at a dose of 120 mg for doublet combination therapy (either Aza or venetoclax) and 80 mg for triplet combination therapy (Aza + venetoclax + gilteritinib).

Cost: Monotherapy with 120 mg of gilteritinib for 1 month will cost INR 6.3 lakh.

Ongoing Phase 3 Trials

Gilteritinib versus midostaurin in combination with intensive chemotherapy for upfront AML and MDS (HOVON 156 AML trial).[15]

Important Points about Gilteritinib[15]

1. Inhibition of *FLT3* needs to be near complete and sustained for days, not hours. Gilteritinib has a long half-life—hence, once daily dosing. It is important to minimize drug interruptions.
2. Lower myelosuppression
   KIT and *FLT3* are structurally similar. Gilteritinib selectively inhibits mutated *FLT3*, it has fivefold less activity against wild-type *FLT3* and nil against KIT—hence, lesser myelosuppression compared with other FLT3i.
3. *FLT3-ITD* AML evolves from diagnosis to relapse
   Leukemic cells are dependent on *FLT3-ITD* signaling for survival. This constitutes a small proportion of the total leukemic cell population at the time of diagnosis. However, it is of a large proportion at the time of relapse. Hence, monotherapy works well at relapse, whereas a combination regimen with synergistic cytotoxicity is a better option for therapy upfront.
4. Gilteritinib acts by a combination of apoptosis and terminal myeloid differentiation
   Apoptosis of peripheral blood blasts results in rapid clearance. However, bone marrow (BM) blasts undergo differentiation. This tends to be a slower process. Hence, the attainment of CR is later than conventional chemotherapy and recovery of normal count is also delayed.
5. Clinical endpoint: BM aplasia is avoided with gilteritinib monotherapy; however, count recovery is delayed. Cri + CRh (CR with incomplete hematological recovery + CR with partial hematological recovery) were included as a valid endpoint in clinical trials. This trend is seen with monotherapy with other targeted therapies like the IDH1 and 2 inhibitors as well. CRh has been associated with transfusion independence and lower risk of infections. Thus, it is a clinically relevant endpoint.
6. MRD analysis: Polymerase chain reaction (PCR) is insufficient to analyze MRD in *FLT3*-mutated AML due to the template bias issue. Hence, a high sensitivity PCR-next-generation sequencing combination method is utilized to test MRD. This is currently not available in India.

Molecular Spectrum of Action[16]

Analysis of the molecular makeup of good responders to gilteritinib demonstrates that:

- Good response was seen with those with concomitant DNMT3A, IDH1/2, and WT-1 mutations.
- While the best response was seen with dual-mutated DNMT3A and NPM1.

The impact of FLT3 mutations on response was also assessed:

- Presence of multiple *FLT3-ITD* mutations had no impact on response.
- Longer *FLT3 ITD* length responded better than shorter ITD length.
- High allele ratio *FLT3* (↑allele burden) is known to have poorer prognosis—gilteritinib was superior to chemotherapy. However, it was not able to fully abrogate the poor risk.

Treatment resistance to gilteritinib:

- Failure of gilteritinib therapy can be caused by primary and secondary mechanisms.
- F691L gatekeeper mutations and *RAS/MAPK* pathway gene mutations constitute the most common resistance pathway. They both are mutually exclusive.
- On-target point mutations: *D835*, *F691* (gatekeeper mutation), *N676*, and *FLT-3* juxtamembrane (JMD) *E598D* mutations.
- Off-target mutations in *Ras/MAPK* pathway: *NRAS*, *PTPN11*, and *KRAS*.
- Nongenetic mechanisms like *FGF2*-activated *FGF1* receptor 1 can also contribute.

Conclusion

Gilteritinib is the first oral tyrosine kinase inhibitor approved for the management of AML in the R/R setting. Its tolerance and lack of marrow aplasia makes it an ideal agent for

managing AML patients in an outpatient setting. Ongoing clinical trials in combination therapy and in upfront setting will open broader avenues in the management of *FLT-3*-mutated AML.

Patient Consent
Patient consent is not required.

Funding
None.

Conflict of Interest
None declared.

References

1 Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory *FLT3*-mutated AML. N Engl J Med 2019; 381(18):1728–1740
2 Levis M, Perl AE. Gilteritinib: potent targeting of FLT3 mutations in AML. Blood Adv 2020;4(06):1178–1191
3 Pratz KW, Cherry M, Altman JK, et al. Gilteritinib in combination with induction and consolidation chemotherapy and as maintenance therapy: a phase IB study in patients with newly diagnosed AML. J Clin Oncol 2023;41(26):4236–4246
4 Astellas Pharma US, Inc. Highlights of prescribing information [Internet]. Northbrook, IL: Astellas Pharma US, Inc.; 2018. Accessed April 4, 2025 at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211349s000lbl.pdf
5 McMahon CM, Canaani J, Rea B, et al. Gilteritinib induces differentiation in relapsed and refractory *FLT3*-mutated acute myeloid leukemia. Blood Adv 2019;3(10):1581–1585
6 Levis MJ, Hamadani M, Logan B, et al; BMT-CTN 1506/MORPHO Study Investigators. Gilteritinib as post-transplant maintenance for AML with internal tandem duplication mutation of *FLT3*. J Clin Oncol 2024;42(15):1766–1775
7 Daver N, Perl AE, Maly J, et al. Venetoclax plus gilteritinib for *FLT3*-mutated relapsed/refractory acute myeloid leukemia. J Clin Oncol 2022;40(35):4048–4059
8 Janssen M, Schmidt C, Bruch PM, et al. Venetoclax synergizes with gilteritinib in FLT3 wild-type high-risk acute myeloid leukemia by suppressing MCL-1. Blood 2022;140(24):2594–2610
9 Wang ES, Montesinos P, Minden MD, et al. Phase 3 trial of gilteritinib plus azacitidine vs azacitidine for newly diagnosed FLT3mut+ AML ineligible for intensive chemotherapy. Blood 2022;140(17):1845–1857
10 Maiti A, DiNardo CD, Daver NG, et al. Triplet therapy with venetoclax, FLT3 inhibitor and decitabine for FLT3-mutated acute myeloid leukemia. Blood Cancer J 2021;11(02):25
11 Abuasab T, Kantarjian H, Garcia-Manero G, et al. Phase II study of cladribine, idarubicin, cytarabine (CLIA) plus gilteritinib in patients with FLT3 mutated acute myeloid leukemia (AML). Blood 2021;138(supplement 1):2330
12 Numan Y, Abdel Rahman Z, Grenet J, et al. Gilteritinib clinical activity in relapsed/refractory FLT3 mutated acute myeloid leukemia previously treated with FLT3 inhibitors. Am J Hematol 2022;97(03):322–328
13 Gyan E, Minden MD, Kubo K, et al. Maintenance therapy with the FMS-like tyrosine kinase 3 inhibitor gilteritinib in patients with FMS-like tyrosine kinase 3-internal tandem duplication acute myeloid leukemia: a phase 2 study. Cancer 2025;131(04):e35746
14 Shatilova A, Budaeva I, Matvienko Y, et al. Myeloid sarcoma or extramedullary acute myeloid leukemia: experience in managing single-centre patients cohort. Blood 2024;144(supplement 1):5987
15 HOVON Foundation. Gilteritinib versus midostaurin in FLT3 mutated acute myeloid leukemia. ClinicalTrials.gov Identifier: NCT04027309. Amsterdam: HOVON; 2018 [updated June 13, 2023]. Accessed April 08, 2025 at: https://clinicaltrials.gov/study/NCT04027309
16 Smith CC, Levis MJ, Perl AE, Hill JE, Rosales M, Bahceci E. Molecular profile of FLT3-mutated relapsed/refractory patients with AML in the phase 3 ADMIRAL study of gilteritinib. Blood Adv 2022;6(07): 2144–2155