



DRUG INFORMATION OF GILTERITINIB AND ITS EFFICACY IN REFRACTORY FLT3-MUTATED AML

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ABSTRACT

Acute myeloid leukemia is a malignancy of proliferative, abnormally, or poorly differentiated cells of the hematopoietic system, characterized by genetic heterogeneity. FMS-like tyrosine kinase 3- internal tandem duplication remains one of the most frequently mutated genes in acute myeloid leukemia, especially in those with normal cytogenetics. The FMS-like tyrosine kinase 3- internal tandem duplication and FLT3 tyrosine kinase domain mutations are biomarkers for high-risk acute myeloid leukemia and are associated with drug resistance and high risk of relapse. Various FLT3 inhibitors are in clinical development, including lestaurtinib, tandutinib, quizartinib, midostaurin, gilteritinib, and crenolanib. Gilteritinib is a small molecule that inhibits multiple receptor tyrosine kinases that also act as FMS-like tyrosine kinase 3. Gilteritinib, a next-generation tyrosine kinase inhibitor, is approved in several countries worldwide for the treatment of relapsed or refractory acute myeloid leukemia in adults with FMS-like tyrosine kinase 3 mutations. Gilteritinib demonstrated the ability to inhibit FLT3 receptor signaling and production in cells exogenously expressing FLT3 including FLT3 internal tandem duplication and tyrosine kinase domain mutations FLT3-D835Y and FLT3-ITD-D835Y, and it induced apoptosis in leukemic cells possessing FLT3 internal tandem duplication. In conclusion, gilteritinib therapy led to higher percentages of patients with the response and longer survival than salvage chemotherapy among patients with relapsed or refractory FLT3-mutated acute myeloid leukemia.

Keywords: Acute myeloid leukemia, FMS-like tyrosine kinase 3- internal tandem duplication, FLT3 tyrosine kinase domain mutations, Gilteritinib, FMS-like tyrosine kinase 3 mutations.

1. INTRODUCTION:

Gilteritinib is first oral FDA approved agent which is available under the brand name Xospata and dosage of 40mg oral tablet[1] It belongs to the class Antineoplastic; Tyrosine kinase inhibitor.[2] Gilteritinib is a pyrazine carboxamide derivative synthesized and developed by Astellas Pharma, Inc. TOKYO; JAPAN.[3]

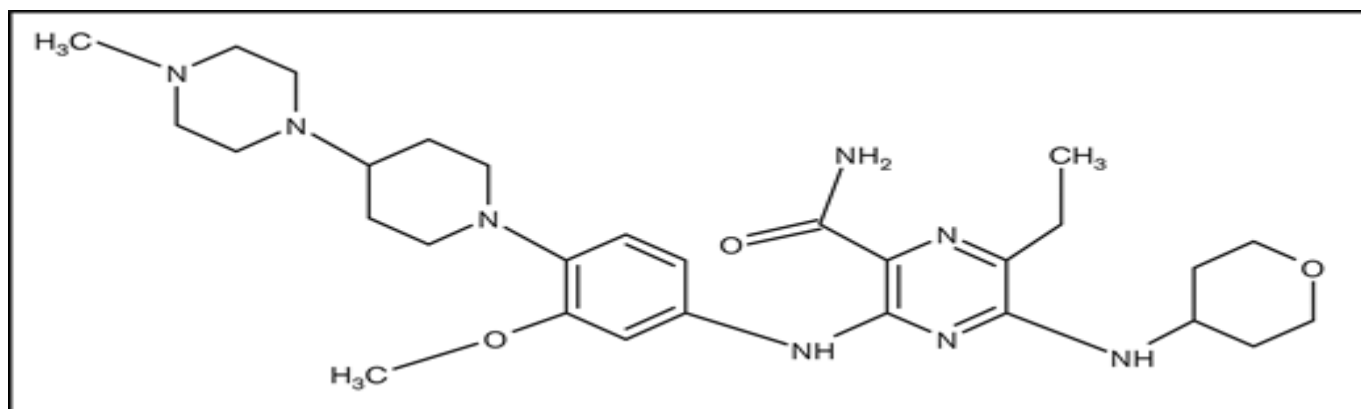


Figure 1: Molecular structure of Gilteritinib

A. MECHANISM OF ACTION:

Gilteritinib is a small molecule that inhibits multiple receptor tyrosine kinases, including FMS like tyrosine kinase 3 (FLT3). It is an orally bioavailable inhibitor of the receptor tyrosine kinases (RTKs) FMS-related tyrosine kinase 3 (FLT3, STK1, or FLK2), AXL (UFO or JTK11) and anaplastic lymphoma kinase (ALK or CD246), with potential antineoplastic activity. Gilteritinib binds to both forms i.e.; wild-type and mutated forms of FLT3, AXL and ALK and also inhibits the both forms. This may result in an inhibition of FLT3, AXL, and ALK-mediated signal transduction pathways and reduces tumor cell proliferation in cancer cell types that overexpress these RTKs. FLT3, AXL and ALK, overexpressed or mutated in a variety of cancer cell types, play a key role in tumor cell growth and survival.[4-7] It is Indicated for management of patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation and prescribed 120 mg orally quarterly in a day. Response may be delayed and hence required to continue for at least 6 months for a clinical response or until disease progression or unacceptable toxicity.[8][9]

B. DOSAGE MODIFICATIONS:

For ADVERSE DRUG REACTIONS:

- For Posterior reversible encephalopathy syndrome (PRES): Terminate the treatment
- QTc interval >500 msec: Withheld the treatment; resume at 80 mg when QTc interval returns to within 30 msec of baseline or ≤480 msec
- QTc interval increased by >30 msec on ECG on Day 8 of Cycle 1: Draw the ECG on Day 9; if confirmed, consider reducing dose to 80 mg
- Pancreatitis: Withheld the treatment until pancreatitis resolved; resume at 80 mg
- Other Grade ≥3 drug-related toxicity: Withheld until toxicity resolves or improves to Grade 1; resume at 80 mg
- Differentiation syndrome
 - If suspected, administer the systemic corticosteroids and initiate hemodynamic monitoring until symptoms resolve for at least 3 days
 - Interrupt dose if severe signs and/or symptoms persist for >48 hr after initiation of corticosteroids
 - Resume when signs and symptoms improve to Grade ≤2

For RENAL OR HEPATIC INPAIRMENT:

- Mild or moderate ([CrCl 30-80 mL/min] or [Child-Pugh Class A or B]): No clinically effects on the pharmacokinetics of gilteritinib
- Severe ([CrCl <30 mL/min] or [Child-Pugh C]): Unknown[10-12]

Assessment of blood cell counts and chemistries prior to initiation, at least quarterly a Week for the first month, once every other week for the second month, and once monthly subsequently perform ECG prior to beginning of management, on Days 8 and 15 of Cycle 1, and prior to the next 2 subsequent cycles.

Selection of patient should be based on

- FLT3 mutation in blood or bone marrow
- Information on FDA-approved tests for FLT3 mutation detection in AML.[13-15]

C. PHARMACODYNAMICS

In preclinical trials, gilteritinib reveal an IC50 for the wild-type receptor of 5 nM, 0.7-1.8 nM for ITD-mutated and comparable inhibition to other therapies in the TKD-mutated. Additionally, data showed a gilteritinib-driven inhibition of the receptor tyrosine kinase AXL which is acknowledged to modulate the activity of FLT3 in acute myeloid leukemia.[16] Another important result in vivo was the localization in high levels in xenografted tumors which indicated high selectivity.[17] In phase 1/2 clinical trials, gilteritinib was shown to present a composite complete response of about 40%, an overall response rate of 50-52%, a median duration of response of 20 weeks with a median overall survival of 31 weeks.[18] In phase III clinical trials, gilteritinib reported a complete remission or complete remission with partial hematologic recovery in 21% of the patients.[19]

D. PHARMACOKINETICS

Absorption involves that in preclinical trials, the maximal plasma concentration of gilteritinib was observed 2 hours after oral administration and followed by a maximal intratumor concentration after 4-8 hours. The steady-state plasma level is reached within 15 days of dosing with an approximate 10-fold bioaccumulation. In a fasted state in humans, the tmax is reported to be of 4-6 hours. The Cmax was decreased by 26% and AUC by 10% by the co-administration of a high-fat meal with a tmax delay of 2 hours.[20] The estimated apparent central and peripheral volume of distribution is 1092 L and 1100 L respectively. This value indicated an extensive tissue distribution.[21] Gilteritinib is reported to be highly bound to plasma proteins, representing 94% of the dose. Therefore, main protein-bound is serum albumin. Gilteritinib is primarily metabolized in the liver by the enzyme activity of CYP3A4. Its metabolism is driven by reactions of N-dealkylation and oxidation which forms the metabolite M17, M16 and M10. As of the plasma concentration, unchanged drug is major form. [22] From the administered dose, gilteritinib is mainly excreted in feces which represents 64.5% of the administered dose while 16.4% is recovered in urine either as the unchanged drug or as its metabolites. The reported median half-life of gilteritinib is of ~45-159 hours. The estimated clearance of gilteritinib is 14.85 L/h. [23]

E. ADVERSE EFFECTS:

Myalgia, increased transaminases, fatigue, fever, dyspnea, edema, noninfectious diarrhea, rashes, pneumonia, constipation, nausea, stomatitis are some of the major reactions that occur after administration.

F. TOXICITY:

Gilteritinib is not mutagenic in bacterial mutagenesis assays nor clastogenic in aberration test assays in Chinese hamster lung cells. However, it resulted positive for the induction of micronuclei in mouse bone marrow and for the degeneration and necrosis of germ cells and spermatid giant cell formation in testis as well as single cell necrosis of the epididymal duct epithelia.[23]

2. FLT3 AND AML:

FLT3 mutations are one of the most common mutations in patients with newly diagnosed acute myeloid leukemia (AML). Patients with relapsed or refractory AML with mutations in the FMS-like tyrosine kinase 3 gene (FLT3) infrequently have a response to salvage chemotherapy. Gilteritinib is an oral, very potent alongside with selective FLT3 inhibitor with single-agent activity in relapsed or refractory FLT3-mutated AML. Approximately 25% to 35% of newly diagnosed younger patients (<65 years) with AML harbor an FLT3 mutation.[24,25] There are 2 major types of FLT3 mutations—internal tandem duplication (FLT3-ITD) and kinase-activating mutation D835 (FLT3-D835)—that are present in about 20% to 30% and 7% to 10% of patients with newly diagnosed AML, respectively. FLT3-mutated AML often presents with proliferative features including elevated white blood cell (WBC) and blast counts at presentation and are associated with adverse outcomes due to short remission durations and early relapse.

2.1. FLT3: The target

The receptor tyrosine kinase (RTK) FLT3 is a member of the alleged “split kinase” type 3 family of RTKs. This involves the homology with KIT, the platelet-derived growth factor receptors, and colony stimulating factor-1 receptor.[26] Thereby, FLT3 inhibitors will often inhibit one or more of these other family members. FLT3’s major role in haematopoiesis is at the progenitor level, where its energy is the expansion of different subsets within this compartment. The FLT3 is vital in haematopoiesis but exact role that it plays in defining specific progenitor cell types continues to be discussed.[27-30] Thereby, it is clear that as the blood cells mature, most lose expression of FLT3, with the exception of dendritic cells, which remain at slightest partially dependent on FLT3 for proliferation.[31] The effect of FLT3 inhibition on any of the progenitor populations is still undistinguishable, as activation of redundant pathways might compensate for the loss of FLT3 signalling. FLT3 is a cytokine receptor, and its cognate ligand, FLT3 ligand is expressed.[32] Finally, the dependence of mature dendritic cells on FLT3 signalling may have implications for patients treated with FLT3 inhibitors. Inhibition of dendritic cell function could result in increased infection risk, mainly in patients who have undergone allogeneic transplant and are receiving an FLT3 inhibitor as maintenance therapy.

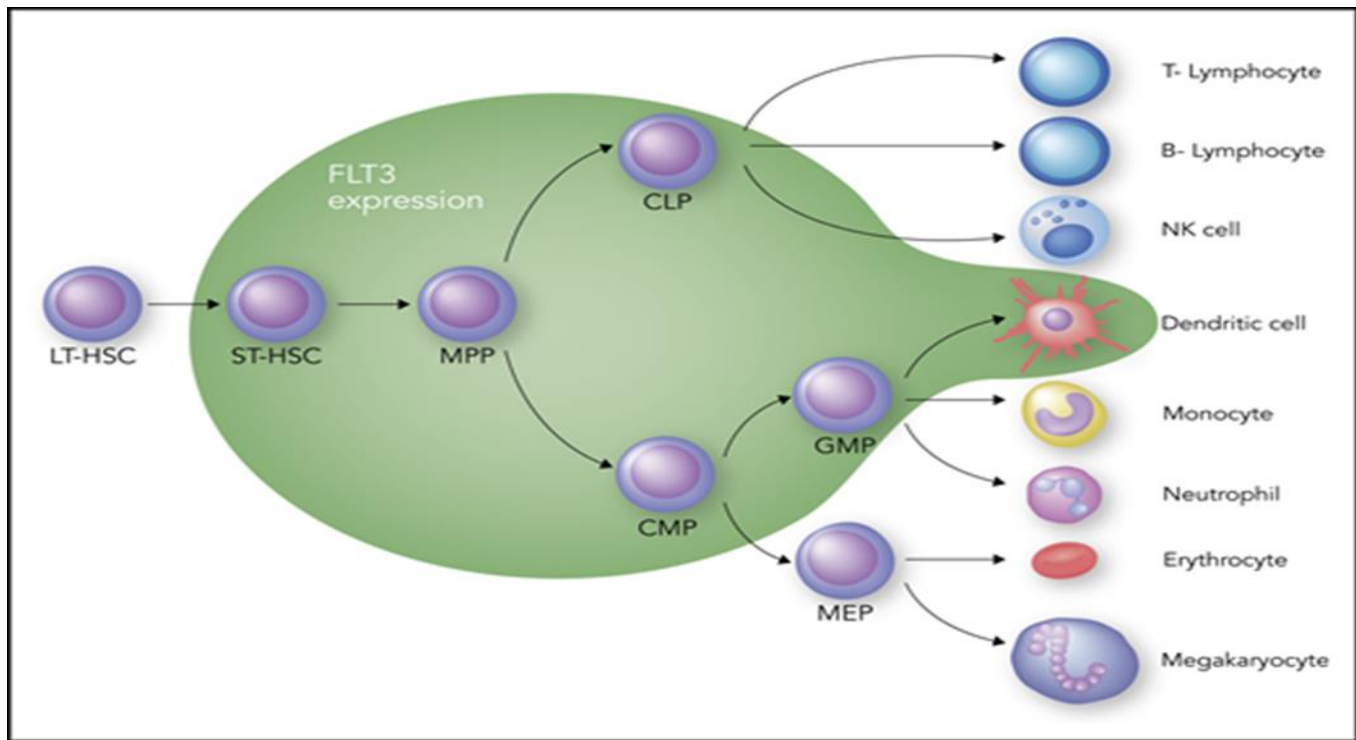


FIGURE 2: Hematopoiesis and FLT3 expression. The green zone surrounds the cell types that express FLT3. CLP, common lymphoid progenitor; CMP, common myeloid progenitor; GMP, granulocyte-macrophage progenitor; LT-HSC, long-term hematopoietic stem cell; MEP, megakaryocyte-erythroid progenitor; MPP, multipotent progenitor; NK, natural killer; ST-HSC, short-term hematopoietic stem cell. Professional illustration by Somersault18:24.

An FLT3-ITD mutation consists of a duplication of coding sequence that is inserted in tandem and in-frame.[33] The length may vary. The duplication almost invariably starts within the juxta membrane domain, generally involving residue arginine 595.[34] Every so often, there is an additional inserted sequence that is unique typically coding for a single amino acid. The juxta membrane domain normally employs a negative regulatory effect on the kinase activity of FLT3, such that structural perturbations these tandem duplications of juxta membrane coding sequence and release the receptor from autoinhibition.[35] The not only the length is variable component of this mutation but the insertion site also vary in turn to the variation in length. A short duplication is generally confined to the juxta membrane domain coding sequence although a longer duplication extends into the first kinase domain, meaning the insertion site is actually within the coding sequence for the kinase domain. These longer insertions are further problematic to detect and almost certainly have a different aggressive phenotype.[36-39] Patients with longer insertions appear to have decreased benefit from the combination of midostaurin and induction/consolidation chemotherapy.[40]

The retrospective studies have shown that the negative prognostic effect of FLT3-ITD mutations recognized the amount of mutant allele relative to the wild-type i.e.; nonmutated allele was important.[41] The capillary electrophoresis method of separating polymerase chain reaction (PCR) products permitted for the calculation of an allelic ratio. Though it is probably safe to conclude that the more FLT3-ITD alleles present, the worse the disease. Present assay methods are not standardized, intrasample variability is high,[37] and consequences may well be influenced by chemotherapy and transplant regimens, which widely vary. Therefore, the Standardization of the FLT3-ITD detection assay is a prior aim in this field of the study. However, In some studies expressed that the unique length of any patient's insertion mutation provides a sign of that patient's disease. Combination PCR-NGS assays appear to yield important information about FLT3-ITD MRD in ongoing studies of FLT3 inhibitors.[42-45] Multiple tyrosine kinase inhibitors (TKIs) have demonstrated clinical activity in FLT3-mutated patients, including midostaurin, sorafenib, crenolanib, gilteritinib, and quizartinib.[46] Where first-generation FLT3 inhibitors (FLT3i's) are lacking in specificity for FLT3 (e.g., midostaurin and sorafenib), second-generation FLT3i's (e.g., crenolanib, gilteritinib, and quizartinib) appear to be more potent and specific, with fewer toxicities and off-target effects. FLT3-targeted TKIs are classified into type I and type II; type I FLT3i binds an active receptor conformation (midostaurin, crenolanib, and gilteritinib) and type II FLT3i binds to the inactive conformation (quizartinib, sorafenib, and ponatinib). Type I inhibitors impinge on FLT3 signaling in AML cells harboring either ITD and/or tyrosine kinase domain (TKD) mutations, whereas type II inhibitors have demonstrated limited to no effect on FLT3-D835 AML cells in culture.[47] Midostaurin, a first-generation type I FLT3i, showed improved overall survival (OS) and improved complete remission (CR) rates when it was added to the backbone of standard AML 3+7 induction therapy compared to 3+7 with placebo in FLT3-mutated (ITD and/or D835) patients in the randomized, multinational, phase 3 RATIFY study.[48,49,50] This led to the approval of midostaurin in combination with induction therapy in newly diagnosed patients with AML who were considered fit for induction therapy in the United States as well as Europe. In the relapsed AML setting, sorafenib, also a first-generation but type II FLT3i, used in combination with the hypomethylating agent (HMA) azacitidine has shown response rates of 40% to 45%, leading to the National Comprehensive Cancer Network (NCCN) guideline for the use of azacitidine with sorafenib in relapsed FLT3-ITD AML.[51] Although midostaurin and sorafenib showed activity in combination with 3+7 induction and azacitidine, respectively, they have very limited single-agent activity, with less than 10% single-agent marrow remission rates in relapsed FLT3-mutated AML based on phase 1 published data.[52] In contrast, the second-

generation FLT3i's gilteritinib and quizartinib have shown clinical efficacy as single agents with composite complete remission (CRc) rates of 45% to 55% in multiple phase 2 trials in relapsed/refractory (r/r) FLT3 mutated AML, highlighting the striking difference in potency between the first- and second-generation FLT3i's.[53,54]

2.2. EFFORTS TO DEVELOP FLT3 INHIBITORS ANINTRODUCTION TO GILTERITINIB:

The encouraging response rates and tolerability with the second-generation FLT3i gilteritinib in the phase 2 CHRYSALIS trial[55] In r/r FLT3 (ITD and/or D835)-mutated patients led to the phase 3 ADMIRAL trial—the focus for this discussion. This was a multicenter, randomized, phase 3 study that enrolled 371 FLT3-mutated (ITD and/or D835) patients randomized 2:1 to be treated with the single-agent FLT3i gilteritinib vs investigator choice (IC) therapy, which included a choice of high-intensity therapy (fludarabine, cytarabine [Ara-C], granulocyte-colony stimulating factor [G-CSF], and idarubicin [FLAG-IDA] or mitoxantrone, etoposide, and cytarabine [MEC]) or low-intensity therapy (HMA or low-dose cytarabine). The co-primary end points of the study were response measured by CR/CR with partial hematologic recovery (CRh) rate and OS. The study met both primary end points with a CR/CRh rate of 34% compared with 15% and a median OS of 9.3 vs 5.6 months with gilteritinib vs IC therapy. The 1-year OS with gilteritinib was 37% compared with 16% with IC therapy. These results clearly showed the superior efficacy of targeted therapy with an FLT3i over cytotoxic or nonspecific lower-intensity therapies in relapsed FLT3-mutated AML. Conceptually, the study was a major breakthrough, showing that—similar to what has been demonstrated in a number of solid tumors—the identification and optimal targeting of driver mutations is a highly effective approach in optimizing management of patients with AML. This was the first randomized phase 3 study to show that single-agent targeted therapy could beat intensive chemotherapy in patients with AML and heralds a paradigm shift in our approach to AML.[56]

The overall marrow remission rates were significantly higher with gilteritinib at 54% compared with 22% with IC chemotherapy. Similarly, the ability to proceed to allogeneic stem cell transplantation—likely the only option with curative potential—was significantly increased in patients who received gilteritinib vs IC chemotherapy. In parallel, another phase 3 study using an alternative second-generation FLT3i, quizartinib, similarly showed improved OS with quizartinib compared with IC therapy in patients with relapsed FLT3-ITD mutated AML.[30] This led to the approval of quizartinib in Japan, but the agent is not approved in the United States or Europe. These studies together confirm the need to routinely check for FLT3 mutations at the time of relapse and, if identified, preferentially select an FLT3-targeted therapy. It is worth noting that FLT3 is a dynamic mutation and has been shown to be acquired at relapse in patients who did not have a detectable FLT3 mutation at baseline or could be lost at relapse in patients who did have a baseline FLT3 mutation. So testing for FLT3 at the time of actual relapse is essential.[57,58]

The improved response rates and survival seen with gilteritinib, while encouraging, leave room for significant improvement. The median OS was 9.3 months, and at 24 months less than 15% of patients remained alive. Evaluating second-generation FLT3i's in the frontline setting in combination with induction therapy or with HMA such as azacytidine may further improve the response rates and duration of response based on recent data and be a more optimal way to use targeted therapies. Similarly, a preclinical synergy of venetoclax, a BCL2 inhibitor, together with gilteritinib has led to a clinical trial combining these 2 agents, and early preliminary data show very high marrow remission rates (>80%).[11] Such novel combinations of FLT3i's with other active AML therapies will likely significantly improve the impact of these therapies and, once optimized, would have the potential to enable us to dramatically improve long-term survival in these r/r AML patients with FLT3 mutations.[59] It had a generally favorable safety and efficacy profile in a population enriched with relapsed/refractory AML. As a result, Gilteritinib is rapidly becoming the standard of care for patients with relapsed or refractory Flats mutated AML.

3. CONCLUSION:

Gilteritinib resulted in significantly longer and higher percentile of patients survival rate involving the with remission than salvage chemotherapy of patients with relapsed or refractory FLT3-mutated AML. Gilteritinib is the first FDA – approved agent and an orally available tyrosine kinase inhibitor for the treatment of relapsed and/or refractory FLT3 mutated AML. FLT3-ITD mutations are associated with highly proliferative disease, shorter duration of remissions and increased rates of diseases. It is important to evaluate the presence of FLT3 mutations throughout the therapy process as there is a greater impact of FLT3 mutations on clinical outcomes. Gilteritinib is able to inhibit both FLT3-ITD and FLT3- TKD mutations that resulted in significantly longer survival and higher percentages of patients with remission than salvage chemotherapy among patients with relapsed or refractory FLT3-mutated AML. The data from the ADMIRAL study has established Gilteritinib as the new standard therapy for RR/ FLT6 mutated AML. It had a generally favorable safety and efficacy profile in a population enriched with relapsed/ refractory AML. As a result, Gilteritinib is rapidly becoming the standard of care for patients with relapsed or refractory Flats mutated AML.

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