Review Article

# Ziftomenib (KOMZIFTI): A New Horizon in Acute Myeloid Leukemia (AML) Treatment

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**ABSTRACT**

The unchecked growth of immature myeloid cells found in blood and bone marrow is the hallmark of AML, or acute myeloid leukemia an aggressive hematological cancer. Targeted medicines that target particular genetic drivers of leukemia have been developed as a result of recent developments in molecular oncology. For individuals with NPM1-mutated AML, ziftomenib, a new menin inhibitor, offers a viable treatment option. This medication reduces leukemic gene transcription and encourages the differentiation of malignant cells by interfering with the menin–KMT2A interaction. The mechanism of action, pharmacology, clinical evidence, safety profile, and potential future therapeutic uses of ziftomenib in the management of AML are all highlighted in this review article.

**Keywords:** Acute Myeloid Leukemia (AML), Ziftomenib, Menin Inhibitor, NPM1-Mutated AML, Targeted Therapy, Menin–KMT2A Interaction, Molecular Oncology.

## INTRODUCTION

Acute myeloid leukemia (AML) is a rare malignancy of the blood and bone marrow. It typically happens when specific genes or chromosomes change. AML can hit youngsters and younger adults, although most usually affects those 60 years of age and older. Acute myeloid leukemia is an aggressive cancer that can be lethal. Thanks to more advanced treatments, people with AML are surviving longer.

Ongoing research to enhance these treatments focuses on targeted medicines and immunotherapies, which can provide patients more customized alternatives.

As a result, the prognosis for AML patients is constantly evolving, providing promise for better outcomes in the future. The goal of this study is to provide an overview of current developments in molecular etiology, diagnostic assessment, and novel therapy approaches.[11]

With a focus on recently created targeted therapeutics for acute myeloid leukemia, this review attempts to provide an overview of recent developments in the molecular etiology, diagnostic assessment, and novel treatment modalities. [12]

**AML subtypes consist of:**

Myeloid leukemia is a kind of cancer that affects cells that produce neutrophils, a type of white blood cell. Most AML patients have the myeloid leukemia subtype. Acute monocytic leukemia (AML-M5) is a type of cancer that affects cells that produce monocytes, a type of white blood cell.

Acute megakaryocytic leukemia (AMLK) is a type of cancer that affects cells that produce red blood cells or platelets. The disease known as acute promyelocytic leukemia (APL) stops promyelocytes, or immature white blood cells, from developing. [14]

**Indication of AML:**

Early signs of AML may resemble a chronic cold or the flu. The course of acute myeloid leukemia is violent. This suggests that they quickly develop additional, more noticeable symptoms. Subsequent symptoms and indicators include:

- Light headedness
- Easy bleeding or bruising, including bleeding gums and nosebleeds.
- Weariness.
- Being chilly.
- A fever.
- Sweats during night.
- Recurring or persistent infections.
- Headaches.
- A decrease in hunger.
- Loss of weight that isn't explained. The skin is pale.
- Dyspnea, or shortness of breath.
- Enlarged lymph nodes.
- Weakness.
- Abdominal, back, or bone pain.
- Petechiae, or little red spots on your skin.
- Persistent wounds or sores.[16]

**Causation**

The cause of acute myeloid leukemia is unknown to experts. They are aware that aberrant blood cells are produced when specific genes or chromosomes mutate.

These genetic alterations could occur: When the human genome is altered during your lifetime. if there's a hereditary disorder that increases a person's susceptibility to AML. if specific genes in the sperm or egg of your biological parents were altered.[18]

**Genetic basis of AML**

The manner in which AML is result of genetic alterations knowing more about the blood cell and bone marrow may help to aid that genetic alterations develop AML. The pliable, spongy substance in the middle of the majority of the bones is called bone marrow. It produces: Immature stem cells develop into oxygen-carrying red blood cells. Defence against infection offers by white blood cell. The blood clots with the aid of platelets. Bone Marrow usually produces the precise quantity of blood cells and platelets that the body requires to function, much like an effective production line. However, in AML, aberrant myeloid cells known as myeloid blasts or myeloblasts are produced by the bone marrow.[20]

Myeloid blasts behave differently from regular blood cells. Genetic instructions dictate when and how fast normal cells should divide and proliferate. As cells age, they die to make space for new cells in the bone marrow. Myeloid blasts are unpredictable. They don't die and proliferate uncontrollably. There is less space for healthy bone marrow blood cell as a result of constant discharge of myeloid blasts. Blood cell are no longer produce by marrow because there is no more space. The body lacks the new, healthy blood cells are essential for healthy operation.[21]

Additionally, when the myeloid blasts continue to proliferate, they start to leak into the circulatory system from the bone marrow. Myeloid cells enter the bloodstream and move to the brain, spinal cord, and central nervous system (CNS), among other sections of the body.[22]

**Diagnostic Strategies of Acute Myeloid Leukemia**

A peripheral blood smear examines a sample of blood for changes in blood cell shape, blast cells, platelet counts or white blood cell counts and types, and platelet counts.[22]

The quantity of cells in a sample, the proportion of living cells in a sample, and specific cell properties including size, shape, and the presence of tumor (or other) markers on the cell surface are all measured by flow cytometry. After being stained with a fluorescent dye and submerged in a liquid, the cells from a sample of a patient's blood, bone marrow or other tissue are individually exposed to a light beam. The way the fluorescent dye-stained cells respond to the light beam determines the test findings. This test aids in the identification and management of several malignancies, including lymphoma and leukemia.[22]

A hollow needle is placed into the hipbone or breastbone to remove bone marrow fluid, blood, and a small bone fragment during a bone marrow aspiration and biopsy. Under a microscope, a pathologist examines the bone, blood, and bone marrow for indications of malignancy.[22]

A tumor biopsy involves using a needle to remove tissues or cells from a mass. This might be carried out if the physician believes the leukemia cells may have transformed into a solid tumor known as a myeloid sarcoma (also called as a chloroma).[22]

Cytogenetic analysis looks for chromosomal abnormalities, such as damaged, missing, altered, or additional chromosomes, in cells obtained from blood or bone marrow samples. Chromosome abnormalities may indicate the existence of cancer. Cancer diagnosis, therapy planning, and treatment efficacy are all aided by cytogenetic analysis. For detecting specific chromosomal alterations, further procedures like fluorescence in situ hybridization (FISH) may be performed.[22]

Molecular testing examines a blood or bone marrow samples for certain genes, proteins, or other substances. Additionally, molecular testing look for specific alterations in a gene or chromosome that could impact the likelihood of developing AML. A molecular test are useful for prognostication, therapy planning, and assessment of treatment efficacy.[22]

Antibodies are utilized during immunophenotyping to detect cancer cells according to the kinds of markers or antigens on their surface. Certain forms of leukemia can be diagnosed with the aid of this test. For example, a cytochemistry investigation might use chemicals (dyes) to analyze the cells in a tissue sample in order to detect specific alterations in the sample. One form of leukemia cell may change colour in response to a chemical, but another type of leukemia cell may not.[22]

The amount of a genetic material called mRNA produced by a particular gene is measured using the reverse transcription–polymerase chain reaction test (RT-PCR). A certain segment of RNA is transformed into a corresponding segment of DNA by an enzyme called reverse transcriptase, which can then be amplified (produced in vast quantities) by another enzyme known as DNA polymerase. The increased DNA copies aid in determining if a gene is producing a certain mRNA. Certain genes that may be indicative of the existence of cancer cells can be checked for activation using RT-PCR. This test may be used to search for specific chromosomal or gene alterations that could aid in the diagnosis of cancer. Acute promyelocytic leukemia (APL) and other forms of AML are identified with this test.[22]

**Hematological and Bone Marrow Examination in AML (Acute Myeloid Leukemia)**

Tests are performed after an AML diagnosis to determine whether the malignancy has spread to other bodily parts. To determine whether leukemia has extended beyond the blood and bone marrow, the following procedures and various tests can be used:[22]

Cerebrospinal fluid (CSF) can be extracted from the spinal column by lumbar puncture.

To extract a CSF specimen, a needle is inserted in the lining around spinal cord and between two bones in the spine. Under a microscope, the CSF sample is examined for indications that leukemia cells have spreads to brain and spinal cord. This procedure also known is an LP or spinal tap.[22]

ENLARGE lumbar puncture: the illustration depicts a patient curled up on a table with a spinal needle—a long, thin needle—inserted into the lower back. A close-up of the spinal needle placed into the CSF (Cerebrospinal fluid) in the lower section of the spinal column is shown in the inset.[22]

A CT scan (CAT scan) creates a sequence of detailed images of internal body parts, like the abdomen, using a computer connected to an x-ray machine. The images, which are captured from various perspectives, are utilized to produce three-dimensional representations of tissues and organs. To make the organs or tissues more visible, a dye can be ingested or injected into a vein. Computed tomography, computerized tomography, or computerized axial tomography are other names for this process. Find out more about cancer and computed tomography (CT) scans.[22]

**Pathophysiology of AML**

Clonal growth and halted maturation of hematopoietic stem cells and progenitor cells comprise the fundamental pathophysiology of AML. Leukemia stem cells, which are multipotent, highly proliferative, and capable of self-renewal, are produced as a result of the first alterations. As a result, more mutations can be acquired. [1] A genomic investigation of 1540 AML patients showed 5234 driver mutations in 76 genes or genomic areas; 96% of the patients had driver mutations, and 86% had two additional driver mutations. [5] Subgroups having the following genetic abnormalities were included in the proposed genomic classification by these researchers. NPM1 mutation.[22]

Chromatin and/or RNA-splicing gene mutations Chromosome aneuploidy and/or TP53 mutations Inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MY11 t(15;17)(q22;q12); PML–RARA RUNX1–RUNX1T1; t(8;21)(q22;q22) MLL fusion genes: t(x;11)(x;q23)GATA2, MECOM(EVI1); inv(3)(q21q26.2) or t(3;3)(q21;q26.2) Mutations in IDH2R172 DEK–NUP214; t(6;9)(p23;q34)[22]

Two disease processes are caused by the alterations in the bone marrow. First, there is a significant reduction in the generation of normal blood cells, which leads to variable degrees of neutropenia, thrombocytopenia, and anemia. Second, the aberrant myeloblasts accumulate in the bone marrow, blood, and often the spleen and liver because to their fast proliferation and decreased capacity for programmed cell death (apoptosis).[22]

**Management of AML Acute Myeloid (Acute Myeloid Leukemia)**

Chemotherapy is the main form of treatment for the most AML cases, occasionally in conjunction with a targeted specific treatment medication.

A stem cell transplant could come next. Acute promyelocytic leukemia (APL), a subtype of AML, can be managed using drugs other than traditional chemotherapy medicines. Although they are not the main treatments for AML, radiation therapy and surgery may be helpful in some situations.[4]

Use of Chemotherapy for Acute Myeloid Leukemia (AML)[4]

Targeted treatment medications for Acute Myeloid Leukemia (AML)[4]

Non-Chemotherapy medications for Acute Promyelocytic Leukemia (APL)[4]

Surgical management of Acute Myeloid Leukemia (AML)[4]

Radio Therapy for Acute Myeloid Leukemia (AML)[4]

Stem Cell Transplantion for Acute Myeloid Leukemia (AML)[4]

**Use of Chemotherapy for AML (Acute Myeloid Leukemia)**

Chemotherapy, often known as chemo, is the use of anti-cancer medications administered orally to eradicate or manage cancer cells, or injected under the skin, into a vein, or into the cerebrospinal fluid (CSF). These medications enter the bloodstream and reach every part of the body except when administered into the CSF, which makes this treatment beneficial for diseases like leukemia that spread throughout the body.[22]

**Chemotherapy Strategies in Acute Myeloid Leukemia (AML)**

The majority of chemotherapy medications for treating AML are administered intravenously (IV), typically via a central venous catheter, however some are injected subcutaneously or taken orally. Chemotherapy may also be delivered into the Cerebrospinal fluid (known as intrathecal chemotherapy) if there are indications that leukemia cells have extend to the brain or spinal cord (which is uncommon with AML). An Ommaya reservoir, a dome-shaped device that rests just beneath the scalp, can be used to insert a thin tube (catheter) via a small opening in the skull. Alternatively, chemotherapy could be administered with a lumbar puncture procedure (spinal tap).[22]

Most chemotherapy treatment regimens for AML are intensive and can cause serious side effects, so treatment typically is administered in the hospital.[22]

**Chemotherapeutic Agents used in Acute Myeloid Leukemia (AML)?**

The chemotherapy medication drugs used most often to treat AML are a combination of:

Cytarabine, also known as cytosine arabinoside (ara-C) and

An anthracycline medication, such as daunorubicin (daunomycin) or idarubicin

**Adverse Effects of Chemotherapy for Acute Myeloid Leukemia (AML)**

Certain healthy cells in the body may be impacted by chemotherapy medications, which may result in adverse effects. The kind, dosage, and duration of the medication will all affect the negative effects. Among the possible side effects are:

• Loss of hair Mouth sores

• A decrease in appetite

• Vomiting along with nausea

• Diarrhea and constipation

• The healthy cells in bone marrow are also impacted by chemotherapy medicines, which can decrease the number of blood cells.

This may result in:

• A greater risk of infection (due to insufficient normal white blood cells)

• Frequent bleeding or bruising (due to insufficient blood platelets)

• Breathing difficulty and tiredness because of reduce red blood cell level

• The requirement for platelet or transfusions red blood cell.[22]

**FLT3 inhibitors in the treatment of AML (Acute Myeloid Leukemia)**

Some AML patients have leukemia cells with genetic change in the FLT3 gene. Normally, this gene aids in the production of a protein (also known as FLT3) that promotes cell growth; when this gene is altered, the cell produces more of this protein. Certain leukemias cases can be managed using drugs that target the FLT3 protein.

It is possible to screen for a FLT3 mutation in your leukemia cells. If so, one of the medications could be beneficial. FLT3 inhibitors such as quizartinib (Vanflyta) and midostaurin (Rydapt), can be used in conjunction with specific chemotherapy medications to treat newly diagnosed patients whose leukemia cells contain a change in the FLT3 gene.[22]

**Side Effects of FLT3 Inhibitors**

● Fever

● Reduced white blood cell counts (higher risk of infection)
● Vomiting and feeling

● Diarrhea

● Mouth sores or redness Pain in the muscles or bones

● A headache Results of abnormal liver tests Infections of the respiratory system[22]

**IDH inhibitors in the treatment of AML (Acute Myeloid Leukemia)**

IDH1 or changes in the IDH2 genes are present in the leukemia cells of certain AML patients. These genes, also known as IDH1 and IDH2, aid in the production of specific proteins by the cells. Blood cells may not mature normally if one of these genes is mutated. IDH proteins can be blocked by targeted medications known as IDH inhibitors. These medications appear to function by assisting the leukemia cells in differentiating into more normal cells. They are sometimes also known as differentiation agents as a consequence of this.[22]

An IDH1 inhibitor called olutasidenib (Rezlidhia) can be given to treat AML with an IDH1 mutation that recurs after treatment or stops responding to previous therapies. IDH2 inhibitors include enasidenib (Idhifa). It can be given to treat AML with an IDH2 mutation, either as the first treatment for patients who are too old or unwell to handle potent chemotherapy, or as a treatment for AML that returns after treatment or stops responding to conventional therapies. One or two times a day, these medications are taken orally.[22]

**Adverse Effects of IDH inhibitors**

IDH inhibitors frequently cause the following adverse effects: ● Vomiting and nausea ● Diarrhea ● Weariness ● Joint discomfort Breathlessness Elevated bilirubin levels (a bile-derived chemical) ● Appetite loss.[22]

**Menin inhibitor in the treatment of Acute Myeloid Leukemia**

Leukemia cells from some AML patients contain either a mutation in the NPM1 gene or a translocation in the KMT2A gene. The KMT2A protein can attach to another protein called menin due to either of these gene changes, which promotes cell growth. Menin inhibitors include revumenib (Revuforj). It prevents menin from joining the KMT2A protein. If AML is not responding to treatment anymore or has returned (relapsed) after previous therapies, this medication can be used to treat patients whose leukemia cells carry an NPM1 mutation or a KTM2A translocation. One of the gene alterations can be detected in your leukemia cells by testing the bloodstream or bone marrow.[22]

**Common side effects of revumenib include:**

● Vomiting or nausea ● Bleeding Constipation or diarrhea ● Weariness ● Muscle pain ● Arm and leg swelling ● Appetite loss.[22]

**Gemtuzumab Ozogamicin (MYLOTARG) in the treatment of AML (Acute Myeloid Leukemia)**

A monoclonal antibody, a synthetic immunological protein, is used along with a chemotherapy drug in the targeted treatment.

After entering the body, the antibody binds to CD33, a protein present on the majority of AML cells. The chemotherapy medicine is delivered to the leukemia cells by the antibody, which functions as a homing device. Once within the cells, it kills them when they attempt to proliferate. When treating AML with the CD33 protein, this medication can be administered in conjunction with chemotherapy. Additionally, it can be administered alone if other therapies are no longer effective or as the initial treatment (particularly in patients who might not be well enough for intensive chemotherapy).. It is administered through an intravenous (IV) infusion.[22]

**Adverse effects of Gemtuzumab Ozogamicin**

Gemtuzumab ozogamicin frequently causes the following adverse effects:

- A fever
- Vomiting and nausea
- Reduce blood cell counts, which increase the risk of infection, bleeding, and exhaustion
- Oral sores and swelling
- Constipation
- Rash
- Headaches[22]

**BCL-2 inhibitors in the treatment of AML (Acute Myeloid Leukemia)**

Venetoclax (Venclexta) targets BCL-2, a protein in cancer cells that allows them to survive longer than normal. This drug can be used with chemo in people recently diagnosed with AML who are 75 years or above, or who cannot tolerate intensive chemotherapy. It's taken by mouth once a day.[22]

**Adverse Effect of Venetoclax**

Venetoclax frequently causes the following adverse effects: Neutropenia, or low amounts of certain white blood cells

- Anemia, or reduced red blood cell levels
- Diarrhea
- Nausea
- Low platelet levels (thrombocytopenia: easy bruising and bleeding) I'm exhausted.[22]

**Supportive surgical interventions in AML (Acute Myeloid Leukemia)**

Surgery has a very limited role in treating acute myeloid leukemia (AML). Leukemia cannot be cured by surgery since leukemia cells are spread throughout the blood and bone marrow. Even for diagnosing AML, surgery is rarely used because a bone marrow aspiration and biopsy are usually adequate.[22]

A thin flexible tube known as a central venous catheter (CVC), also referred to as a central line or venous access device, is frequently inserted into a major vein in the chest prior to the initiation of chemotherapy for AML.A surgeon in the operating room or a particular kind of radiologist could perform this. The tube's end either protrudes in the upper arm or chest or remains slightly beneath the skin. In order to administer intravenous (IV) medications, such as chemotherapy, and to collect blood samples for testing, the CVC can be remained in place during treatment (often for several months). As a result, fewer needle sticks are required during treatment.[22]

**Role of Radiation Therapy in AML (Acute Myeloid Leukemia)**

High-energy radiation is used in radiation treatment to destroy cancer cells. Although there are a few situations where it might be employed, it is typically not a part of the primary treatment for patients with acute myeloid leukemia (AML).[22]

**Radiation Therapy Techniques in AML (Acute Myeloid Leukemia)**

The radiation experts will carefully measure the angles at which the radiation beams should be aimed as well as the appropriate radiation dose before your treatment begins. Typically, imaging tests like CT or MRI scans are part of this planning session, also known as simulation.[22]

External beam radiation is the kind of radiation therapy used to treat AML. The procedure is similar to receiving an x-ray, but the radiation is far more potent. The actual process is painless. The purpose of radiation therapy determines how many treatments you receive. Although the setup time—getting you in position for treatment—usually takes longer, each treatment only lasts a few minutes.[22]

**Adverse Effects of Radiation Treatment for AML (Acute Myeloid Leukemia)**

Depending on where the radiation is directed, radiation therapy may have adverse effects.

- The treated area may have sunburn-like skin changes and hair loss.
- Mouth sores, dry mouth, and difficulty swallowing can result from radiation exposure to the head and neck region.
- Abdominal radiation exposure might result in nausea, vomiting, or diarrhea.
- Radiation can cause fatigue by lowering blood counts.[22]

**Role of stem cell transplantation in AML (Acute Myeloid Leukemia)**

Higher doses of chemotherapy than would typically be administered can occasionally be administered by doctors using a stem cell transplant (SCT). (Radiation therapy is occasionally administered for AML as well.) Following treatment, the patient receives a blood-forming stem cell infusion to replenish their bone marrow.[3]

Blood or bone marrow can provide the blood-forming stem cells needed for a transplant. Stem cells from a baby's umbilical cord are occasionally utilized.[3]

Depending on the source of the blood-forming stem cells, stem cell transplants (SCT) vary.

**New Horizon in Pharmacotherapy of Acute Myeloid Leukemia**

Ziftomenib (Komzifti), a menin inhibitor, was approved by the Food and Drug Administration on November 13, 2025, for people with refractory or relapsed acute myeloid leukemia (AML) who have a susceptible nucleophosmin 1 (NPM1) mutation and no other effective therapy choices.[6]

Generic name: Ziftomenib

Brand name: **KOMZIFTI**

Manufacturer: Kura Oncology, Inc, San Diego, California

Class: Menin inhibitor

Date of approval by the US Food and Drug Administration (FDA): November 13, 2025

Cost: US$ per month: 48,500 (wholesale acquisition cost)

**Indication**

Adult patients with relapsed or treatment-resistant acute myeloid leukemia (AML) who have a susceptible nucleophosmin 1 (NPM1) mutation and no other effective therapy choices may be treated with ziftomenib, a menin inhibitor.[1]

**PHAMACODYNAMICS**

**Mechanism of Action**

A menin inhibitor called ziftomenib prevents menin from interacting with lysine [K]-specific methyltransferase 2A (KMT2A) proteins.[10]

Mutations in NPM1 that attract the wild-type menin-KMT2A complex to leukemogenic gene promoters can cause acute leukemias. The term "susceptible NPM1 mutations" refers to mutations that cause the nucleolar localization signal to be lost and a new nuclear export signal to be inserted. This causes mutant NPM1 protein to accumulate in the cytoplasm, disrupting normal cell function and causing leukemogenesis through altered gene expression.[10] Ziftomenib's pharmacologic disruption of the menin-KMT2A protein–protein interaction inhibits the oncogenic activity of mutant NPM1, which causes leukemic cells to differentiate as shown by elevated expression of differentiation markers. Ziftomenib demonstrated both in vitro and in vivo anticancer efficacy in NPM1-mutant leukemia models in nonclinical investigations.[10]

**Unwanted Effects**

Differentiation syndrome (rapid myeloid cell proliferation and differentiation), QTc interval prolongation, and embryo-fetal damage are among the cautions and warnings.

Infection without an identified pathogen (15%), differentiation syndrome (13%), febrile neutropenia (5%), pyrexia (4%), ECG QT prolonged (4%), leukocytosis (4%), bacterial infection (3%), cardiac failure (2%), cholecystitis (2%), diarrhoea (2%), pruritus (2%), and thrombosis (2%) were among the adverse reactions that necessitated dose interruption in ≥2% of patients.[14]

**Dosage**

KOMZIFTI should be taken once day on an empty stomach at a dose of 600 mg until the disease progresses or toxicity becomes intolerable. Wait until the white blood cell count is below 25 × 109/L before beginning KOMZIFTI. It is advised that patients receive treatment for at least six months in order to give time for a clinical response if there is no evidence of disease progression or intolerable toxicity.[6]

**Nature of Evidence**

An open-label, single-arm, multicenter trial called KO-MEN-001 (NCT04067336) evaluated efficacy in 112 patients with relapsed or refractory AML who had an NPM1 mutation found by next-generation sequencing or polymerase chain reaction. Type A, B, and D variants as well as other NPM1 mutations that could result in the NPM1 protein localizing in the cytoplasm were among the patients with NPM1 mutations that were included.[14]

Efficacy was assessed using the duration of CR + CRh, the rate of conversion from transfusion dependence to transfusion independence, and the rate of complete remission (CR) plus CR with partial hematological recovery (CRh). The median follow-up was 4.2 months (range: 0.1–41.2 months). The rate was 21.4% (95% CI, 14.2–30.2) and the duration of CR + CRh was 5 months (95% CI, 1.9–8.1). The CR rate was 17.0% (95% CI, 10.5–25.2), whereas the CRh rate was 4.5% (95% CI, 1.5–10.1).[14]

During any 56-day post-baseline period, 14 (21.2%) Of the 66 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 14 (21.2%) became independent of these treatments during any 56-day post-baseline period. Twelve patients (26.1%) of the 46 people who did not need RBC or platelet transfusions at baseline did not need transfusions in any of the 56 days that followed baseline**.**[14]

**PHARMACOKINETICS**

Absorption is rapid, with a median T max and $Tmax$ of 3.5 hours. Ziftomenib is widely dispersed throughout tissues. Metabolism and Elimination N is mostly broken down by oxidation. Demethylation, as well as N -dealkylation, mostly by CYP3A. The medication can be used once daily due to its lengthy half-life (t 1/2 $t$ 1/2) of 61.5 hours. It is usually eliminated in feces as the parent drug in its unaltered form.[12]

**Storage**

Store at 20-25ºC (68-77ºF); temperature variations are allowed between 15-30ºC (59-86ºF)[7]

## CAUTIONS

### Pregnancy

According to animal studies and its mechanism of action, ziftomenib may cause embryo fetal harm when used during pregnancy.[13]

Advise pregnant women of potential fetal risk.[13]

Verify pregnancy status in women of reproductive potential before initiating.[13]

### Animal Studies

Administration to pregnant mice during organogenesis led to adverse developmental effects, including embryo-fetal death, structural abnormalities, and altered fetal growth at maternal exposures ~0.3x the human exposure (AUC) at recommended dose.[13]

### Contraception

Females of reproductive potential should use effective contraception during treatment and for 6 months following the last dose.[13]

Males with female partners of reproductive potential should use effective contraception during treatment and for 3 months following last dose.[13]

### Infertility

According to animal studies, the drug may impair fertility in both females and males of reproductive potential.[13]

These effects were not reversible after a 4-week recovery period in animal studies.[13]

### Lactation

There is no available data regarding the presence of ziftomenib or its metabolites in human milk or effects on breastfed children or milk production.[13]

Due to the potential risk of adverse reactions in breastfed infants, women are advised not to breastfeed during treatment and for 2 weeks following the last dose.[13]

### Clinical Trial Evidence[11]

| NCT Number | Sponsor | Condition | Start Date | Phase |
|---|---|---|---|---|
| NCT06001788 | Kura Oncology, Inc | AML/AML With Mutated NPM1/Hematologic Malignancy/KMT2Ar/NPM1 Mutation/MLL Rearrangement Leukemia | 2024-02-22 | PHASE1 |
| NCT04067336 | Kura Oncology, Inc. | Advanced Malignant Neoplasm/Acute Myeloid Leukemia/Mixed Lineage Leukemia | 2019-09-12 | PHASE1\|PHASE2 |
| NCT06769490 | M.D. Anderson Cancer center | Acute Myeloid Leukemia (AML) | 2025-06-30 | PHASE1 |
| NCT06930352 | Uma Borate \| Kura Oncology | Acute Myeloid Leukemia | 2025-06-01 | PHASE2 |
| NCT05738538 | Kura Oncology, Inc. | Acute Lymphoblastic Leukemia (ALL) With Appropriate Mutations/Acute Myeloid Leukemia with NPM1 Mutations | | |
| NCT06448013 | M.D. Anderson Cancer Center \| Kura Oncology, Inc. | Acute Myeloid Leukemia | 2025-03-07 | PHASE1 |
| NCT05848687 | Tanja Andrea Gruber \| Pediatric Oncology Experimental Therapeutics Investigators' Consortium \| Amgen \| Lucile Packard Foundation for Children's Health \| Kura Oncology, Inc. | Lymphoblastic Leukemia | 2023-11-03 | PHASE1\|PHASE2 |
| NCT06440135 | Massachusetts General Hospital | Acute Myeloid Leukemia/Acute Myeloid Leukemia in Remission/NPM1 Mutation/KMT2A Rearrangement | 2024-06-06 | PHASE1 |
| NCT05735184 | Kura Oncology, Inc. | Acute Myeloid Leukemia/Mixed Lineage Acute Leukemia/Mixed Lineage Leukemia Gene Mutation | 2023-07-18 | PHASE1 |
| NCT06655246 | Kura Oncology, Inc. | Gastrointestinal Stromal Tumor (GIST)/Gastrointestinal Stromal Tumor of the Gastrointestinal Tract | 2025-03-27 | PHASE1 |
| NCT06376162 | LLS Ped AL Initiative, LLC \| Kura Oncology | Relapsed/Refractory KMT2A-r Acute Leukemia/Relapsed Refractory NUP98-r Acute Leukemia | 2025-03-18 | PHASE1 |
| NCT06397027 | M.D. Anderson Cancer Center \| Kura Oncology, Inc. | Refractory Acute Leukemia/Pediatric Relapsed | 2024-12-27 | PHASE1 |

**Future Directions and Ongoing Research**

Acute myeloid leukemia (AML) treatment has advanced significantly with the development of ziftomenib (Komzifti), especially for individuals with NPM1-mutated illness. However, other therapeutic uses, combination approaches, and long-term effects related to menin inhibition are still being investigated. Future research attempts to increase treatment effectiveness, broaden the range of indications, and get a deeper understanding of the resistance mechanisms connected to this innovative type of targeted therapy.[15]

**1. Extension of Indications**

Researchers are looking at ziftomenib possible significance in additional leukemia subtypes, even though it is only licensed for relapsed or resistant AML with NPM1 mutation.[15]

**2. Strategies for Combination**

Therapy One of the most effective approaches to improve ziftomenib clinical efficacy is combination therapy. Combinations with several established AML therapies are currently being investigated by researchers. [15]

**3. Getting RID of Drug Resistance**

Drug resistance is still a possible problem with most targeted therapy. Resistance mechanisms could include: Secondary mutations that impact the binding location of menin Alternative carcinogenic pathway activation Leukemic cells' epigenetic modifications Developing next-generation menin inhibitors and enhancing therapy results depend on an understanding of these mechanisms.[2]

**4. Creation of Menin Inhibitors of the Next Generation**

Next-generation menin inhibitors are presently being developed by a number of pharmaceutical companies with the following goals: Boost your potency Minimize negative consequences Overcome mechanisms of resistance Patients who relapse after initial menin inhibitor medication may eventually have more treatment options thanks to these more recent drugs.[20]

**5. Development of Biomarkers and Personalized Medicine**

Predictive biomarkers that help to identify patients who are most likely to benefit from ziftomenib therapy are another area of interest for future research. Among the possible biomarkers are: Particular subtypes of NPM1 mutations Signatures of gene expression linked to menin dependency Monitoring for minimal residual disease (MRD) These methods will help AML patients receive a more individualized treatment plan.[15]

**6. Long-term Results Research**

Long-term data on survival outcomes are still being gathered because ziftomenib was only recently licensed.

Future clinical research will assess: Total survival (OS) Survival without progression (PFS)Life quality Long-term security The best location for ziftomenib within AML therapy algorithms will be determined with the use of these data.[15]

## CONCLUSION

A new era in AML treatment based on targeted epigenetic regulation and menin inhibition is ushered in by ziftomenib. Ongoing research is likely to broaden its clinical use, enhance combination strategies, and achieve better outcomes for patients with difficult to treat leukemia.

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