New Drug Overview

Komzifti (ziftomenib)

RDL Category: Antineoplastics

Introduction

Disease Background:

- Acute myeloid leukemia (AML) encompasses a mixed group of aggressive blood cell cancers that happen from clonal expansion of cancerous hematopoietic precursor cells of the bone marrow (*Kolitz 2025*).
  - The leukemic cells affects the creation of normal blood cells, resulting in anemia, infection, and bleeding, among other symptoms and difficulties.
  - *NPM1* mutations and lysine *KMT2A* rearrangements are leukemogenic drivers observed in subsets of AML. The most frequent genetic alterations, observed in close to 30% of newly diagnosed AML cases, includes *NPM1* mutations (*Wang et al 2025*).
- AML, although relatively rare, is generally seen in older adults, with an approximate median age at diagnosis of 68 to 71 years. In adults, it is the most frequent kind of acute leukemia. In the United States, there were approximately 20,800 new AML cases in 2024, described as being 1% of all cancer cases (*Di Nardo et al 2026, Kolitz 2025*).
- While some with AML are asymptomatic and only have laboratory abnormalities, most have clinical symptoms. Clinical presentations may include (*Kolitz 2025*):
  - Signs/symptoms due to anemia (such as weakness, dyspnea), thrombocytopenia (excess bleeding or bruising), and neutropenia (fever, infections) are usual.
  - Headache or focal neurological complaints.
  - Findings such as pallor, bleeding, or bruising.
- Komzifti was FDA approved in 2025.

Pharmacology/Usage

- Komzifti (ziftomenib) is a menin inhibitor.
  - It is a menin inhibitor that blocks the interaction of menin and lysine [K]-specific methyltransferase 2A (KMT2A).
  - Acute leukemias can be driven by mutations in *NPM1* that recruit the wild-type menin-KMT2A complex to promoters of leukemogenic genes. Susceptible *NPM1* mutations are defined as those that result in loss of the nucleolar localization signal and the insertion of a new nuclear export signal leading to cytoplasmic accumulation of mutant NPM1 protein that disrupts normal cell function and drives leukemogenesis through altered gene expression.
  - Pharmacologic disruption of the menin-KMT2A protein-protein interaction by ziftomenib blocks oncogenic activity of mutant NPM1, which induces differentiation of leukemic cells as evidenced by increased expression of differentiation markers.

Indications

Table 1. Food and Drug Administration Approved Indications

Indication	Komzifti (ziftomenib)
• For the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible nucleophosmin 1 (*NPM1*) mutation who have no satisfactory alternative treatment options.	✔

(Prescribing information: Komzifti 2025)

- Information on indications, mechanism of action, pharmacokinetics, dosing, safety, and clinical efficacy summary has been obtained from the prescribing information for the individual products, except where noted otherwise.

Dosing and administration

Table 2. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Komzifti (ziftomenib)	Capsules: 200mg. -Swallow whole; do not open, break, or chew the capsules.	PO	600mg QD until disease progression or unacceptable toxicity. -Do not start until the white blood cell (WBC) count is reduced to less than 25 X 10^9/L. For patients without confirmed disease progression or unacceptable toxicity, treatment for a minimum of 6 months is recommended to allow time for a clinical response.	• Select patients for the treatment of relapsed or refractory AML based on the presence of an *NPM1* mutation. An FDA-approved test for the detection of *NPM1* mutations is not currently available. • Administer on an empty stomach (at least 1 hr before or 2 hrs after a meal). • If a dose is missed or not taken at the usual time, administer the dose as soon as possible on the same day and at least 12 hours prior to the next scheduled dose. Return to the normal schedule the following day. Do not administer 2 doses within 12 hours. • Manage any abnormalities promptly. Interrupt or reduce dose for adverse reactions per the prescribing information. • Dose adjustments are not required with mild or moderate renal impairment; however, the effects of severe

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				renal impairment have not been studied. • Dose adjustments are not required with mild or moderate hepatic impairment. The effects of severe hepatic impairment have not been studied.

See the current prescribing information for full details.

Clinical Efficacy Summary

- The efficacy of Komzifti was assessed in an open-label, single-arm, multicenter clinical trial (Study KO-MEN-001; KOMET-001) in adult patients (N=112) with relapsed or refractory AML with an *NPM1* mutation identified using next-generation sequencing or polymerase chain reactions.
  - Patients with *NPM1* mutations, including Type A, B, and D mutations and other *NPM1* mutations likely to result in cytoplasmic localization of the NPM1 protein, were enrolled.
  - Other eligibility criteria included creatinine clearance ≥30ml/min, total bilirubin ≤1.5 times the upper limit of normal (ULN), aminotransferases ≤2 X ULN, QTcF ≤480 msec, and Eastern Cooperative Oncology Group (ECOG) performance status score of 0-2.
- Komzifti was given at a dose of 600mg QD until disease progression or unacceptable toxicity. Patients were permitted to resume treatment with Komzifti following hematopoietic stem cell transplant (HSCT). Four (3.6%) of the 112 patients underwent stem cell transplantation following Komzifti treatment.
- Demographics and disease characteristics of patients in the study include a median age of 69 years (with 63% being ≥65 years), while 56% were female, 79% were white, 78% were not Hispanic or Latino, and the median number of prior lines of therapy was 2. In addition, 85% had De novo AML.
- Efficacy was established based on the rate of complete remission (CR) plus CR with partial hematological recovery (CRh), the duration of CR+CRh, and the rate of conversion from transfusion dependence to transfusion independence. The median follow-up was 4.2 months.
  - Efficacy results are presented in the table below, which was adapted from the prescribing information. Note that CI=confidence interval.

Table 3. Efficacy results

Endpoint	Komzifti (N=112)
CR+CRh, n (%)	24 (21.4%)
95% CI	(14.2, 30.2)
Median duration of CR+CRh (months)	5.0
95% CI	(1.9, 8.1)
CR, n (%)	19 (17.0%)

Endpoint	Komzifti (N=112)
95% CI	(10.5, 25.2)
Median Duration of CR (months)	5.0
95% CI	(2.8, 8.1)
CRh, n (%)	5 (4.5%)
95% CI	(1.5, 10.1)
Observed Duration of CRh (months)	0.0+, 1.5+, 1.5, 1.6, 11.4

- For patients who achieved a CR or CRh, the median time to first response was 2.7 months (range, 0.9 to 15 months). Of the 24 patients who achieved a response of CR or CRh, 21 patients (88%) did so within 6 months of starting Komzifti.
- Among the 66 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 14 (21.2%) became independent of RBC and platelet transfusions during any 56-day post-baseline period. Of the 46 patients who were independent of both RBC and platelet transfusions at baseline, 12 patients (26.1%) remained transfusion independent during any 56-day post-baseline period.

Clinical guidelines

- **National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Acute Myeloid Leukemia** (*NCCN 2026*).
  - Ziftomenib has been added to the guidelines.
  - Regarding therapy for relapsed/refractory disease in adults, targeted therapy listed for AML with *NPM1* mutation includes revumenib and ziftomenib.

Safety summary

- **Contraindications:** None.

- **Box Warning:**
  - Komzifti has a box warning regarding differentiation syndrome. Differentiation syndrome, which can be fatal, has occurred with Komzifti.
    - Signs and symptoms may include fever, joint pain, hypotension, hypoxia, dyspnea, rapid weight gain or peripheral edema, pleural or pericardial effusions, pulmonary infiltrates, acute kidney injury, and rashes.
    - If differentiation syndrome is suspected, interrupt Komzifti and start oral or intravenous corticosteroids with hemodynamic and laboratory monitoring until symptom resolution; resume Komzifti upon symptom improvement.

- **Warnings and precautions:**
  - Komzifti can cause QT (QTc) interval prolongation.
    - Correct electrolyte abnormalities, including hypokalemia and hypomagnesemia, prior to treatment with Komzifti. Perform an ECG prior to initiation of treatment and do not start Komzifti in patients with QTcF >480msec. Perform an ECG at least once weekly for the first four weeks on treatment, and at least monthly thereafter.

- Interrupt Komzifti if the QTc interval is >500 ms or the change from baseline is >60 ms.
- In patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval, more frequent ECG monitoring may be necessary.
- Concomitant use of Komzifti with drugs known to prolong the QTc interval may increase the risk of QTc interval prolongation.

- **Common adverse drug reactions**:
  - Listed % incidence for adverse drug reactions= reported % incidence for drug (Komzifti) for all grades. There was no placebo data in the prescribing information to compare with.
    - The most frequently reported adverse events included infections without identified pathogen (52%), bacterial infection (28%), viral infection (16%), hemorrhage (38%), hypertension (11%), diarrhea (36%), nausea (35%), fatigue (34%), edema (30%), musculoskeletal pain (28%), differentiation syndrome (26%), pruritus (23%), febrile neutropenia (22%), leukocytosis (16%), transaminases increased (21%), electrocardiogram QT prolonged (12%), renal impairment (19%), and hypoxia (9%).
    - Laboratory abnormalities (Grades 1-4) include aspartate aminotransferase increased (53%), potassium decreased (52%), albumin decreased (51%), alanine aminotransferase increased (50%), sodium decreased (49%), creatinine increased (45%), alkaline phosphatase increased (41%), bilirubin increased (27%), and potassium increased (26%).

- **Drug interactions:**
  - Ziftomenib is primarily metabolized by CYP3A. Concomitant use of Komzifti with strong or moderate CYP3A4 inhibitors increases ziftomenib exposure, which may increase the risk of adverse reactions such as QT prolongation.
    - Monitor patients more frequently with concomitant use of strong or moderate CYP3A4 inhibitors with Komzifti for Komzifti-associated adverse reactions.
  - Ziftomenib is mainly metabolized by CYP3A. Concomitant use of Komzifti with strong or moderate CYP3A4 inducers may decrease ziftomenib exposure, which may reduce the efficacy of Komzifti.
    - Avoid concomitant use of Komzifti with strong or moderate CYP3A4 inducers.
  - Concomitant administration of ziftomenib with proton pump inhibitors (PPIs) decreases ziftomenib exposure, which may reduce the efficacy of Komzifti.
    - Avoid concomitant use of Komzifti with PPIs.
    - Avoid concomitant use of Komzifti with H2 receptor antagonists (H2RAs) or locally acting antacids. If concomitant use cannot be avoided, modify Komzifti administration time.
  - Ziftomenib causes QTc interval prolongation. Concomitant use of Komzifti with other products that prolong the QTc interval may result in a greater increase in the QTc interval and adverse reactions associated with QTc interval prolongation and sudden death.
    - Avoid concomitant use of Komzifti with other product(s) with a known potential to prolong the QTc interval. If concomitant use cannot be avoided, obtain ECGs when initiating, during concomitant use, and as clinically indicated. Interrupt Komzifti if the QTc interval is >500 ms or the change from baseline is >60 ms.

- **Special populations:**
  - There is no pregnancy category for this medication; however, the risk summary indicates that based on findings in animals and its mechanism of action, Komzifti can cause embryo-fetal harm when administered to a pregnant woman. There are no available data on use in pregnant women to assess for a drug-associated risk.
    - Advise pregnant women of the potential risk to a fetus.
    - Verify pregnancy status in females of reproductive potential prior to starting Komzifti.

- Advise females of reproductive potential to use effective contraception during treatment with Komzifti and for 6 months after the last dose.
- Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose.

○ The safety and efficacy of use in the pediatric population have not been established.

Conclusion

- Acute myeloid leukemia (AML) encompasses a mixed group of aggressive blood cell cancers that happen from clonal expansion of cancerous hematopoietic precursor cells of the bone marrow (*Kolitz 2025*).
- Komzifti is a menin inhibitor indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible *NPM1* mutation who have no satisfactory alternative treatment options.
- It has a box warning regarding differentiation syndrome, which has occurred with Komzifti use.
- Komzifti can cause QT(QTc) interval prolongation.
  - ○ Correct electrolyte abnormalities prior to treatment. In addition, perform an ECG prior to starting treatment and do not start Komzifti in patients with QTcF >480msec.
  - ○ Concomitant use with drugs known to prolong the QTc interval may increase the risk of QTc interval prolongation.
- The efficacy of Komzifti was assessed in an open-label, single-arm, multicenter study that included adult patients with relapsed or refractory AML with an *NPM1* mutation.
  - ○ Efficacy was established based on the rate of CR + CRh, the duration of CR + CRh, and the rate of conversion from transfusion dependence to transfusion independence.
    - The endpoint of CR + CRh occurred in 21.4% of Komzifti-treated patients, while the median duration of CR + CRh was 5 months.
- NCCN guidelines were updated in 2026 and include ziftomenib, as well as revumenib (brand name Revuforj), as targeted therapy for AML with *NPM1* mutation in relapsed/refractory disease.

- It is recommended that Komzifti should be non-recommended with conditions in order to confirm the appropriate diagnosis and clinical parameters for use.

- **RDL Placement:**
  - ☐ Recommended
  - ☒ Non-Recommended with Conditions

References

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- Kolitz JE. Acute myeloid leukemia in adults: Overview. UpToDate Website. Updated January 14, 2025. Accessed June 15, 2026. https://www.uptodate.com.
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- Wang ES, Montesinos P, Foran J, et al. Ziftomenib in relapsed or refractory *NPM1*-mutated AML. J Clin Oncol. 2025; 43(31): 3381-3390.

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