Real-World Application of Menin Inhibitors in Patients with Acute Leukemia

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Disclosures

- Off-label (pipeline) treatments will be discussed
- Financial disclosure

Partnership	Activity	Compensation
Takeda Oncology	Advisory Board	Honorarium

Roadmap

1. Available therapies for relapsed/refractory (R/R) Acute Myeloid Leukemia (AML) and Acute Lymphoblastic Leukemia (ALL)
2. Menin inhibition
3. FDA-approved menin inhibitors and published data
4. Patient cases
5. Menin inhibitor toxicities, recommended monitoring, and suggested management
6. Pipeline / future directions

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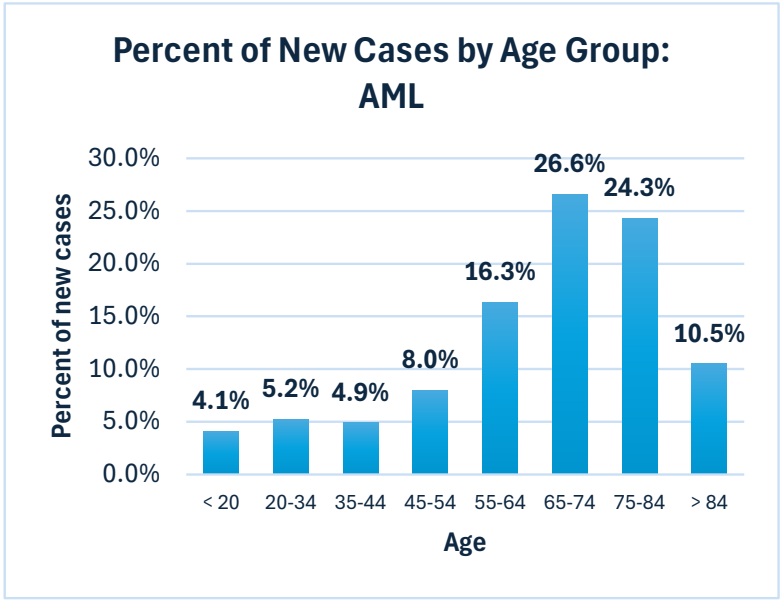
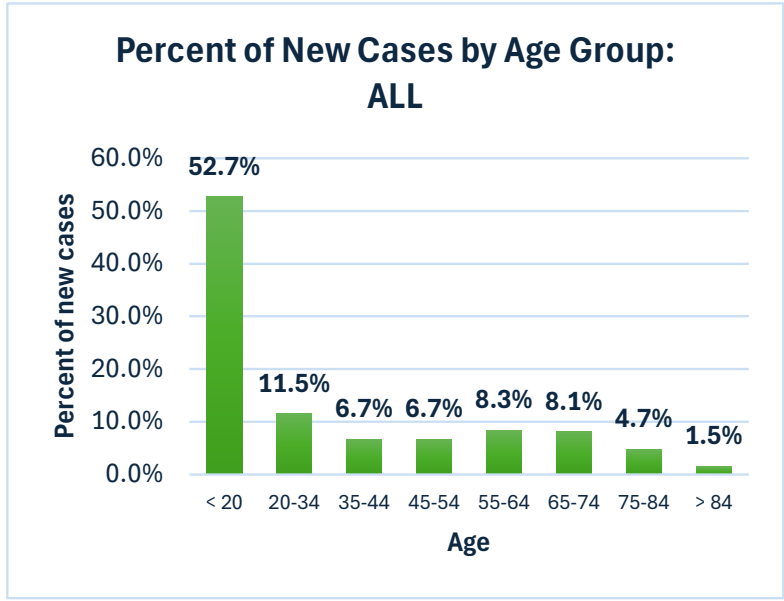
Overview of Acute Leukemias

- Heterogeneous diseases characterized by different phenotypic, genetic, and molecular alterations
- R/R acute leukemias are associated with poor survival, substantial health care resource utilization, and negative effects on quality of life

Statistic	AML	ALL
Estimated new cases in 2025	22,010	6,100
Percentage of all new cancer cases	1.1%	0.3%
Median age at diagnosis, years	69	17
5-year relative survival	32.9%	72.6%
Median age at death, years	74	60
Estimated deaths in 2025	11,090	1,400

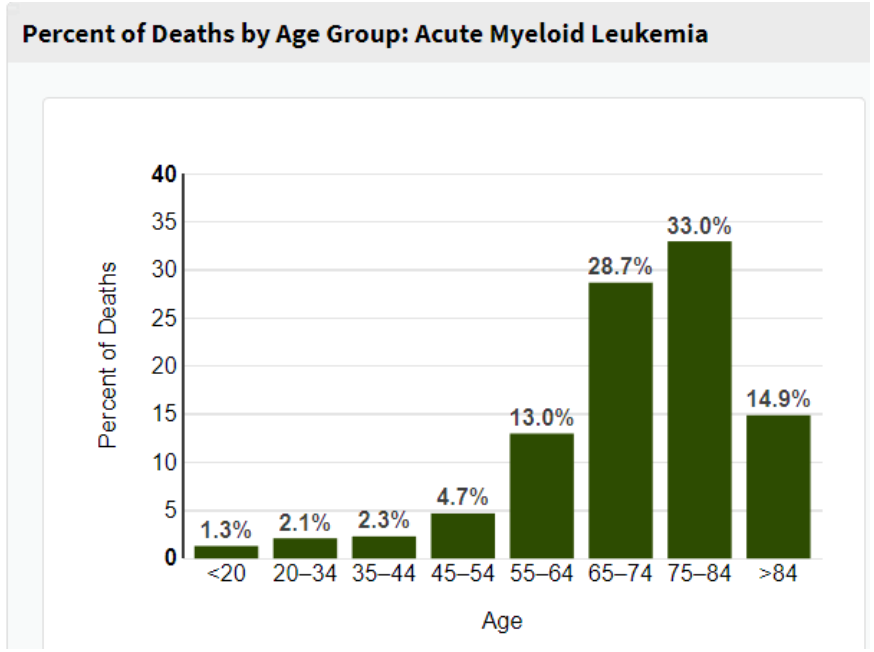


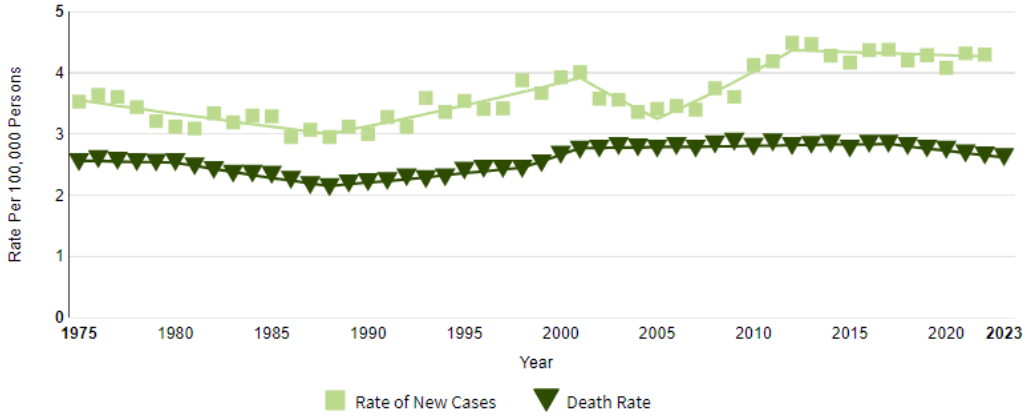


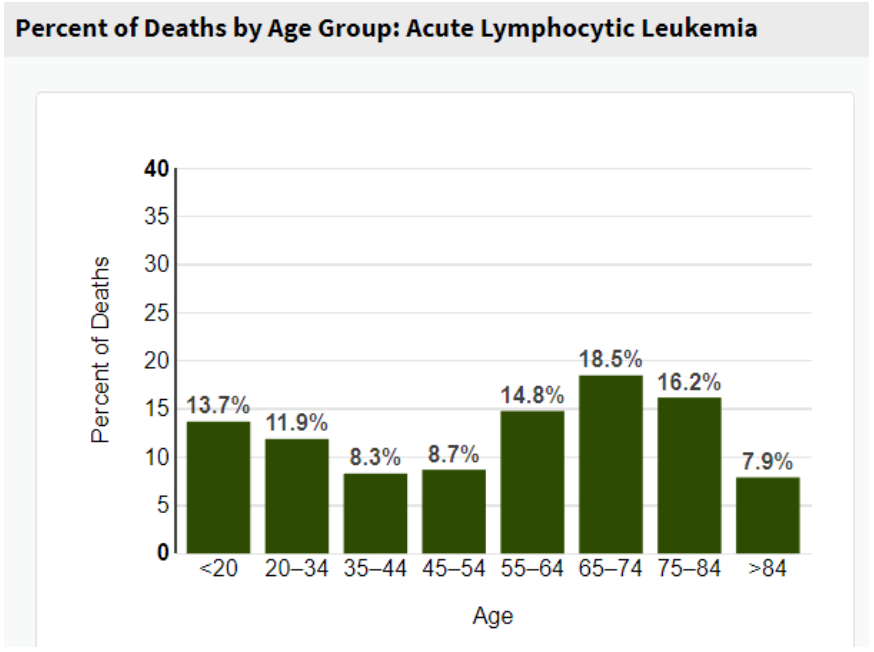
Graphs adapted from Cancer Facts and Figures

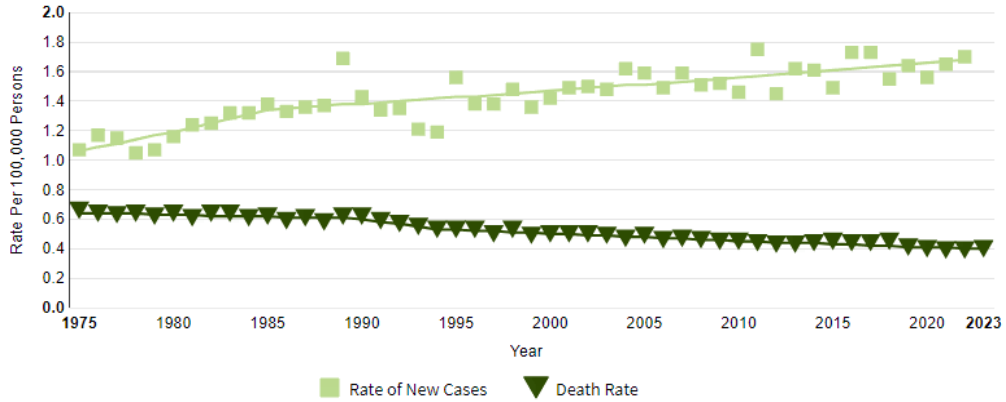
1. Abraham I, Martin P, Vaghela S, et al. Budget impact analysis of revmenib for the treatment of relapsed or refractory acute leukemias with a KMT2A translocation in the United States. *J Manag Care Spec Pharm*. 2025; 31(7): 680-93.
2. Cancer Facts and Figures. American Cancer Society. Available at https://seer.cancer.gov/statfacts/html/amyl.html. Accessed February 14, 2026.
3. Cancer Facts and Figures. American Cancer Society. Available at https://seer.cancer.gov/statfacts/html/alyl.html. Accessed February 14, 2026.

Acute Leukemia Survival









1. Cancer Facts and Figures. American Cancer Society. Available at https://seer.cancer.gov/statfacts/html/amyl.html. Accessed February 14, 2026.
2. Cancer Facts and Figures. American Cancer Society. Available at https://seer.cancer.gov/statfacts/html/alyl.html. Accessed February 14, 2026.

Treatment Options for R/R AML

- Treatment is challenging and outcomes are poor
- Allogeneic hematopoietic cell transplant (HCT) is only curative option

Targeted Therapy

- **FLT3-ITD mutation:** gilteritinib, sorafenib + [azacitidine or decitabine], quizartinib
- **FLT3-TKD mutation:** gilteritinib
- **IDH2 mutation:** enasidenib
- **IDH1 mutation:** ivosidenib, olutasidenib
- **CD33+:** gemtuzumab ozogamicin
- **KMT2A-r:** revumenib
- **NPM1 mutation:** revumenib, ziftomenib

Intensive Therapy

- Cladribine + cytarabine + filgrastim (CLAG) ± [mitoxantrone or idarubicin]
- Cytarabine ± [daunorubicin or idarubicin or mitoxantrone]
- Fludarabine + cytarabine + filgrastim (FLAG) ± idarubicin ± venetoclax
- Etoposide + cytarabine ± mitoxantrone
- Clofarabine ± cytarabine ± idarubicin
- Cladribine + idarubicin + cytarabine (CLIA) + venetoclax

Less Intensive Therapy

- Azacitidine or decitabine
- Low-dose cytarabine
- Venetoclax + [azacitidine or decitabine]

Abbreviations not previously defined:
- FLT3-ITD: FMS-like tyrosine kinase 3 – Internal Tandem Duplication
- FLT3-TKD: FMS-like tyrosine kinase 3 – Tyrosine Kinase Domain
- IDH2: Isocitrate Dehydrogenase 2
- IDH1: Isocitrate Dehydrogenase 1
- KMT2A-r: Lysine Methyltransferase 2A rearrangement
- NPM1: Nucleophosmin 1

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National Comprehensive Cancer Network. Acute Myeloid Leukemia (Version 3.2026). https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Accessed February 13, 2026

Treatment Options for R/R ALL

Ph+ B-cell ALL

- TKI (dasatinib, imatinib, ponatinib, nilotinib, or bosutinib) ± chemotherapy
- Asciminib + dasatinib
- Blinatumomab + TKI
- Inotuzumab ozogamicin ± TKI
- Tisagenlecleucel
- Brexucabtagene autoleucel
- Obecabtagene autoleucel
- Inotuzumab ozogamicin + mini-hyperCVD
- Augmented HyperCVAD
- Clofarabine
- Fludarabine + cytarabine + filgrastim ± idarubicin
- Fludarabine + cytarabine + mitoxantrone
- Alkylating agent combination
- Revumenib (if KMT2A-r)

Ph- B-cell ALL

- Blinatumomab ± chemotherapy
- Inotuzumab ozogamicin
- Tisagenlecleucel
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- Revumenib (if KMT2A-r)

Abbreviations not previously defined:

- Ph: Philadelphia Chromosome
- TKI: Tyrosine Kinase Inhibitor
- Mini-hyperCVD: hyperfractionated cyclophosphamide, vincristine, dexamethasone alternating with cytarabine, methotrexate
- Augmented HyperCVAD: hyperfractionated cyclophosphamide, intensified vincristine, doxorubicin, intensified dexamethasone, pegaspargase; alternating with high-dose methotrexate, cytarabine

T-cell ALL

- Bortezomib-containing regimen
- Daratumumab-containing regimen
- High-dose cytarabine-containing regimen
- Mitoxantrone + etoposide + cytarabine
- Revumenib (it KMT2A-r)
- Nelarabine ± etoposide ± cyclophosphamide
- Venetoclax-containing regimen
- Augmented HyperCVAD
- Clofarabine
- Methotrexate + vincristine + pegaspargase + dexamethasone
- Fludarabine + cytarabine + filgrastim ± idarubicin
- Fludarabine + cytarabine + mitoxantrone
- Cytarabine-containing regimen
- Alkylating agent combination

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National Comprehensive Cancer Network. Acute Lymphoblastic Leukemia (Version 2.2025). https://www.nccn.org/professionals/physician_gls/pdf/all.pdf. Accessed February 13, 2026.

Role of Menin

KMT2A-r

- Also known as mixed lineage leukemia (MLL)
- Occurs in 5-10% of all adult acute leukemias and ~70% of infant leukemias
- Poor prognostic factor
- KMT2A translocations occur with > 80 partner genes, leading to the production of oncogenic fusion proteins
- KMT2A fusion proteins bind to menin, driving aberrant expression of HOX and MEIS1
- HOX/MEIS1 expression activates leukemogenic transcriptional program, leading to block of differentiation

NPM1m

- Most common genetic alteration in adult AML (~20-30% of new diagnoses)
- Favorable prognosis in absence of other mutations
- Binds to KMT2A / menin complex, leading to HOXA9 and MEIS1-driven leukemogenesis

Abbreviations not previously defined:
- HOX: Homeobox
- MEIS1: Myeloid Ecotropic Viral Integration Site 1
- NPM1m: NPM1 mutation or NPM1-mutated
- HOXA9: Homeobox A9

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1. Wenge DV and Armstrong SA. Menin inhibition for the treatment of acute leukemia. *Seminars in Hematology*, 2025 (62): 187-95.
2. Thomas X. Small molecule menin inhibitors: novel therapeutic agents targeting acute myeloid leukemia with KMT2A rearrangement or NPM1 mutation. *Oncol Ther,* 2024 (12): 57-72.
3. Issa GC, Ravandi F, DiNardo CD, et al. Therapeutic implications of menin inhibition in acute leukemias. *Leukemia*, 2021 (35): 2482-95.
4. Kuhn MW, Song E, Feng Z, et al. Targeting chromatin regulators inhibits leukemogenic gene expression in NPM1 mutant leukemia. *Cancer Discov*, 2016; 6(10):1166-81.
5. Uckelmann HJ, Haarer EL, Takeda R, et al. Mutant NPM1 directly regulates oncogenic transcription in acute myeloid leukemia. *Cancer Discov,* 2023; 13(3): 746-65.

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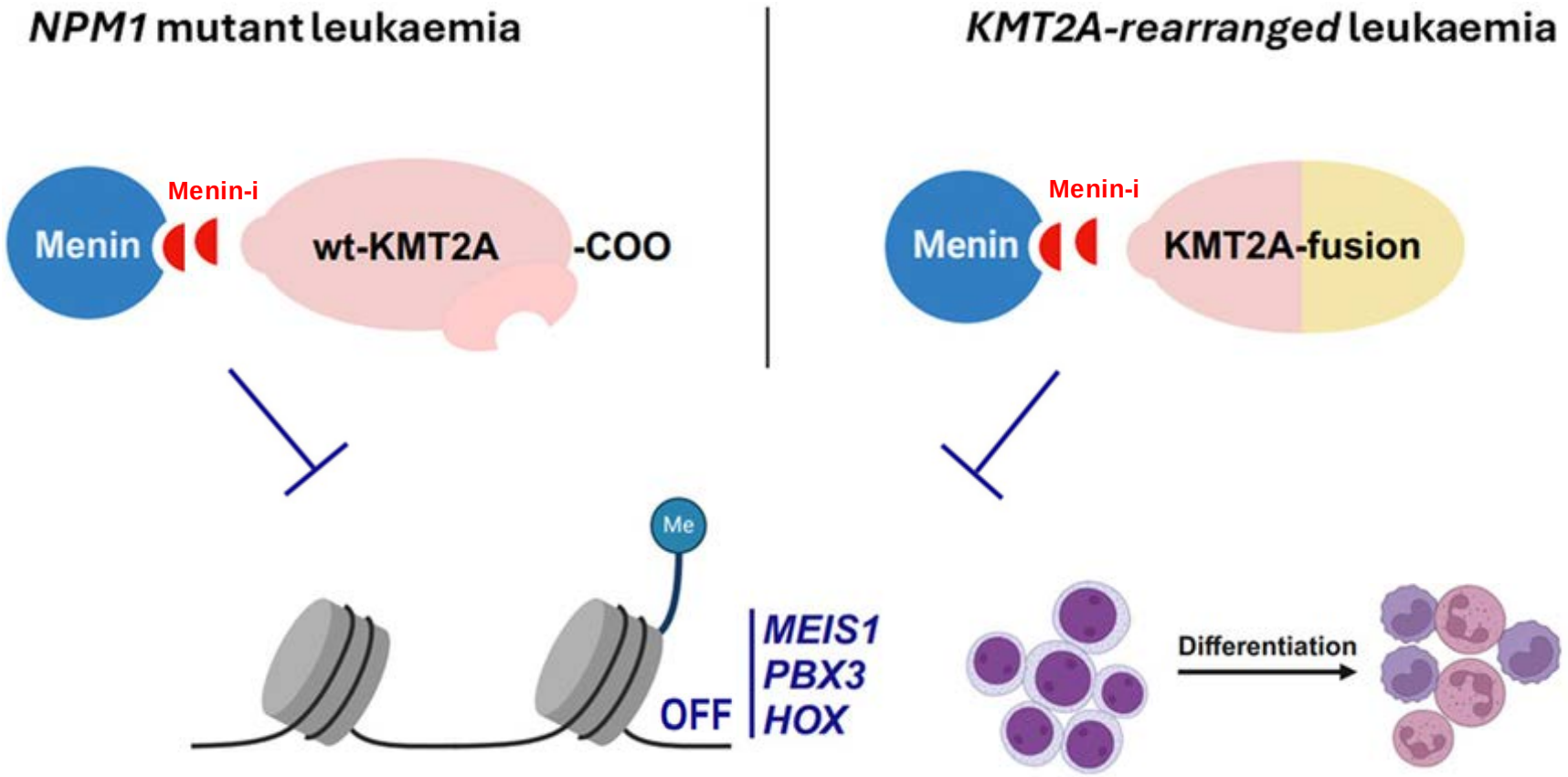
Menin Inhibitors



Abbreviations not previously defined:
- Menin-i: menin inhibitor

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Kuhn MWM, Ganser A. The menin story in acute myeloid leukaemia – the road to success. *British Journal of Haematology,* 2024; 205(3): 812-14.

FDA-Approved Menin Inhibitors

Drug Name	Manufacturer	FDA Approval Date	Indication
Revumenib (Revuforj®)	Syndax	November 15, 2024	R/R acute leukemia with a KMT2A translocation in adult and pediatric patients 1 year and older
		October 24, 2025	R/R AML with a susceptible NPM1 mutation in adult and pediatric patients 1 year and older who have no satisfactory alternative treatment options
Ziftomenib (Komzifti®)	Kura Oncology	November 13, 2025	R/R AML with a susceptible NPM1 mutation in adult patients who have no satisfactory alternative treatment options

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1. Revuforj (revumenib) [prescribing information]. New York, NY: Syndax Pharmaceuticals Inc; December 2025.
2. Komzifti (ziftomenib) [prescribing information]. San Diego, CA: Kura Oncology Inc; November 2025.

FDA-Approved Menin Inhibitors

Drug Name	Starting Dose	Food Impact	Clinically Relevant Drug Interactions (DDIs)
Revumenib (Revuforj®)	Patients ≥ 40 kg: 270 mg (1 x 160 mg tablet + 1 x 110 mg tablet) by mouth twice daily Patients < 40 kg: 160 mg/m^2 by mouth twice daily	Take on an empty stomach, at least 1 hour before or 2 hours after a meal OR Take with a low-fat meal (~400 calories and ≤ 25% fat)	Concomitant strong CYP3A4 inhibitor: o Patients ≥ 40 kg: 160 mg by mouth twice daily o Patients < 40 kg: 95 mg/m^2 by mouth twice daily
Ziftomenib (Komzifti®)	600 mg (3 x 200 mg capsules) by mouth once daily	Take on an empty stomach, at least 1 hour before or 2 hours after a meal	• Avoid proton pump inhibitors (PPI) • Take ziftomenib either 2 hours before or 10 hours after a histamine H2 receptor blocker (H2RA) • Take ziftomenib either 2 hours before or 2 hours after an antacid

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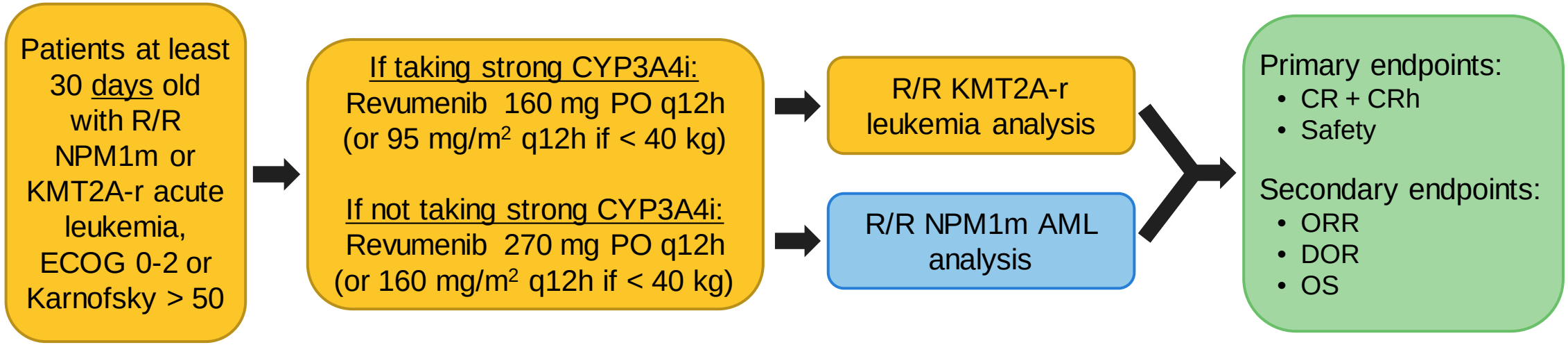
1. Revuforj (revumenib) [prescribing information]. New York, NY: Syndax Pharmaceuticals Inc; December 2025.
2. Komzifti (ziftomenib) [prescribing information]. San Diego, CA: Kura Oncology Inc; November 2025.

Revumenib: AUGMENT-101

- Phase I/II open-label dose-escalation and expansion study
- Phase II design



Abbreviations not previously defined:
- ECOG: Eastern Cooperative Oncology Group
- CYP3A4i: cytochrome P 450 3A4 inhibitor
- PO: by mouth
- q12h: every 12 hours
- CR: complete remission
- CRh: complete remission with partial hematologic recovery
- ORR: overall response rate
- DOR: duration of response
- OS: overall survival

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1. Issa GC, Aldoss I, Thirman MJ, et al. Menin inhibition with revumenib for KMT2A-rearranged relapsed or refractory acute leukemia (AUGMENT-101). *Journal of Clinical Oncology,* 2025; 43(1): 75-84.
2. Arellano ML, Thirman MJ, DiPersio JF, et al. Menin inhibition with revumenib for NPM1-mutated relapsed or refractory acute myeloid leukemia: the AUGMENT-101 study. *Blood*, 2025; 146(9): 1065-77.

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AUGMENT-101: Revumenib KMT2A-r Efficacy Analysis

Baseline Characteristic	KMT2A-r Patients (n=57)
Age, years, median (range)	37 (1.3 – 75)
Female sex, n (%)	33 (57.9)
White race, n (%)	43 (75.4)
Primary refractory, n (%)	14 (24.6)
Relapse refractory, n (%)	32 (56.1)
Type of acute leukemia, n (%) • AML • ALL • Ambiguous lineage	 49 (86) 7 (12.3) 1 (1.8)
Prior lines of therapy, n, median (range) • One • Two • Three or more	 17 (29.8) 14 (24.6) 26 (45.6)
Prior allogeneic HCT	26 (45.6)

Parameter	KMT2A-r Patients (n=57)
ORR, n, (%) [95% CI]	36 (63.2) [49.3 – 75.6]
Time to first response, months, median (range)	0.95 (0.9-2)
DOR, months, median (range)	4.3 (1.9-NR)
CR + CRh, n (%) [95% CI], one-sided *p* value	13 (22.8) [12.7-35.8], 0.0036
CRc, n (%) [95% CI]	25 (43.9) [30.7-57.6]
Best response, n (%) • CR • CRh • CRi • CRp • Morphological leukemia-free state • Partial remission • Progressive disease / no response	 10 (17.5) 3 (5.3) 1 (1.8) 11 (19.3) 10 (17.5) 1 (1.8) 18 (31.6)
MRD negative rate within evaluable patients • Within CR + CRh, n (%) • Within CRc, n (%)	 7 / 10 (70) 15 / 22 (68.2)
Responders who proceeded to HCT, n (%)	14 / 36 (38.9%)
OS, median, months [95% CI]	8 [4.1-10.9]

Abbreviations not previously defined:
- HCT: hematopoietic cell transplant
- CI: confidence interval
- NR: not reported
- CRc: composite complete remission
- CRi: complete remission with incomplete hematologic recovery
- CRp: complete remission with incomplete platelet recovery
- MRD: minimum residual disease

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Issa GC, Aldoss I, Thirman MJ, et al. Menin inhibition with revumenib for KMT2A-rearranged relapsed or refractory acute leukemia (AUGMENT-101). *Journal of Clinical Oncology,* 2025; 43(1): 75-84.

AUGMENT-101: Revumenib NPM1m Efficacy Analysis

Baseline Characteristic	NPM1m Patients (n=64)
Age, years, median (range)	65 (19-84)
Female sex, n (%)	38 (59.4)
White race, n (%)	38 (59.4)
Primary refractory, n (%)	5 (7.8)
Relapse refractory, n (%)	35 (54.7)
Prior lines of therapy, n, median (range) • Three • Four or more	 23 (35.9) 14 (21.9)
Prior allogeneic HCT	14 (21.9)
Co-occurring mutations, n (%) • FLT3-ITD • FLT3-TKD • RAS • TP53	 22 (34.4) 4 (6.3) 2 (3.1) 4 (6.3)

Parameter	NPM1m Patients (n=64)
ORR, n (%) [95% CI]	30 (46.9) [34.3-59.8]
Time to first response, months, median (range)	1.84 (0.9-4.6)
DOR, months, median [95% CI]	4.4 [1.2-5.6]
CR + CRh, n (%) [95% CI], one-sided *p* value	15 (23.4) [13.8-35.7], 0.0014
CRc, n (%) [95% CI]	19 (29.7) [18.9-42.4]
Best response, n (%) • CR • CRh • CRi • CRp • Morphological leukemia-free state • Partial remission • Progressive disease / no response	 12 (18.8) 3 (4.7) 2 (3.1) 2 (3.1) 9 (14.1) 2 (3.1) 21 (32.8)
MRD negative rate	NR
Responders who proceeded to HCT, n (%)	5 / 30 (16.7%)
OS, median, months [95% CI] • All patients • Within CR + CRh	 4 [2.5-7.2] 23.3 [7.2-NR]

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Arellano ML, Thirman MJ, DiPersio JF, et al. Menin inhibition with revumenib for NPM1-mutated relapsed or refractory acute myeloid leukemia: the AUGMENT-101 study. *Blood*, 2025; 146(9): 1065-77.

AUGMENT-101 Safety Results

Select treatment-emergent adverse effects (AE)	R/R Acute Leukemia Patients (n=241), %	
	Any Grade	Grade 3+
Febrile neutropenia	37	35
Hemorrhage	48	10
Thrombosis	11	6
Nausea	48	5
Diarrhea	29	5
Constipation	20	0
Differentiation syndrome (DS)	25	12
QTc prolongation	36	17
Edema	24	0
Infection without identified pathogen	46	30
Musculoskeletal pain	37	6
Increased creatinine	38	2
Decreased potassium	34	12
Increased aspartate aminotransferase (AST)	44	6
Increased alanine aminotransferase (ALT)	40	8

Median duration of exposure: 2.5 months (range < 1 – 40)

- AE leading to dose reduction: 12%
  - QT prolongation
- AE leading to dose interruption: 49%
  - QT prolongation
  - Infection
  - Febrile neutropenia
  - DS
  - Nausea
  - Hypokalemia
- AE leading to treatment discontinuation: 20%
  - Infection
- AE leading to death: 9 (4%)
  - 4 sudden death
  - 2 DS
  - 2 hemorrhage
  - 1 cardiac arrest

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1. Issa GC, Aldoss I, Thirman MJ, et al. Menin inhibition with revumenib for KMT2A-rearranged relapsed or refractory acute leukemia (AUGMENT-101). *Journal of Clinical Oncology,* 2025; 43(1): 75-84.
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3. Revuforj (revumenib) [prescribing information]. New York, NY: Syndax Pharmaceuticals Inc; December 2025.

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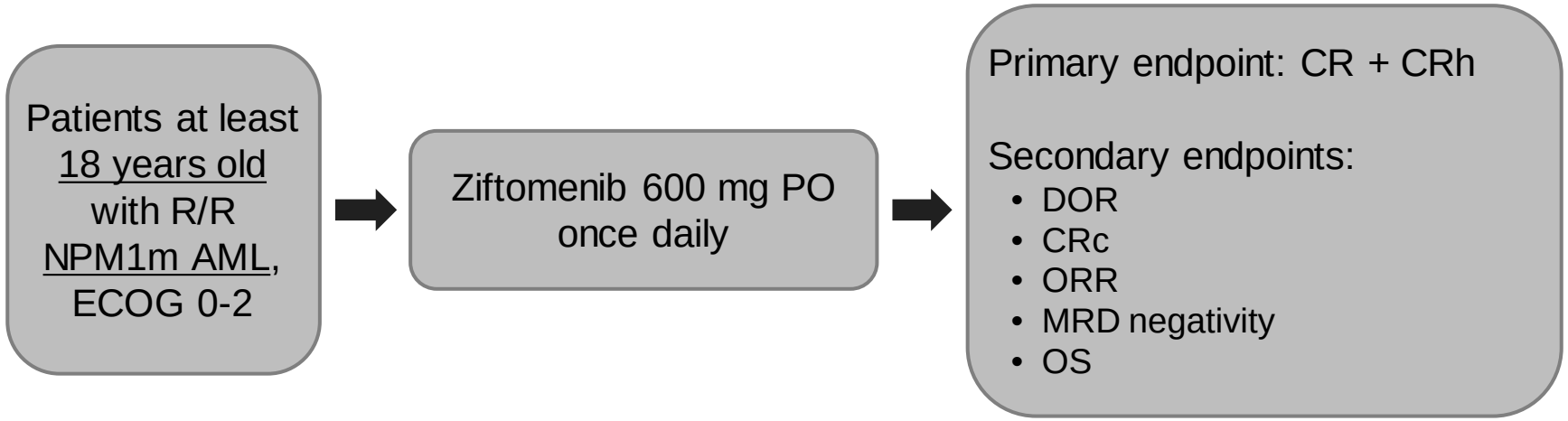
Ziftomenib: KOMET-001

- Phase I/II study
- Phase II design



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Wang ES, Montesinos P, Foran J, et al. Ziftomenib in relapsed or refractory NPM1-mutated AML. *Journal of Clinical Oncology,* 2025; 43(31): 3381-90.

KOMET-001: Ziftomenib NPM1m Efficacy Analysis

Baseline Characteristic	Patients (n=92)
Age, years, median (range)	69 (33-84)
Female sex, n (%)	49 (53)
White race, n (%)	75 (82)
Prior lines of therapy, median, n (range)	2 (1-7)
Prior lines of therapy, n (%)	
• One	32 (35)
• Two	30 (33)
• Three or more	30 (33)
Prior allogeneic HCT	22 (24)
Co-occurring mutations, n (%)	
• FLT3-ITD	38 / 84 (45)
• FLT3-TKD	9 / 84 (11)
• IDH1	10 / 80 (13)
• IDH2	16 / 81 (20)

Parameter	Patients (n=92)
ORR, n (%) [95% CI]	30 (33) [23-43]
Time to first response, median, months (range)	1.9 (0.8-3.7)
DOR, median, months [95% CI]	4.6 [2.8-7.4]
CR + CRh, n (%) [95% CI]	20 (22) [14-32]
CRc, n (%) [95% CI]	24 (26) [18-36]
Best response, n (%)	
• CR	13 (14)
• CRh	7 (8)
• CRi / CRp	4 (4)
• Morphological leukemia-free state	5 (5)
• Partial remission	1 (1)
• Stable disease / no response / progression	46 (50)
MRD negative rate, n (%)	14 / 25 (56)
Responders who proceeded to HCT, n (%)	2 / 30 (7)
OS, median, months [95% CI]	
• All patients	6.6 [3.6-8.6]
• Within CR + CRh	18.4 [8.6-NR]

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Wang ES, Montesinos P, Foran J, et al. Ziftomenib in relapsed or refractory NPM1-mutated AML. *Journal of Clinical Oncology,* 2025; 43(31): 3381-90.

KOMET-001 Safety Results

Select treatment-emergent AE	Patients (n=112), %	
	Any Grade	Grade 3-4
Febrile neutropenia	22	22
Hemorrhage	38	8
Nausea	35	2
Diarrhea	36	5
Differentiation syndrome	26	13
QTc prolongation	12	8
Edema	30	3
Infection without identified pathogen	52	38
Bacterial infection	28	17
Fatigue	34	8
Musculoskeletal pain	28	4
Pruritus	23	0
Increased AST	53	4
Increased ALT	50	6
Increased bilirubin	27	6
Decreased potassium	52	22
Increased creatinine	45	4

Median duration of exposure: 2.2 months (range 0.1 – 21.5 months)

- AE leading to dose reduction: 4%
- AE leading to dose interruption: 54%
  - Infection
  - DS
  - Febrile neutropenia
  - Pyrexia
- AE leading to treatment discontinuation: 21%
  - Infection without identified pathogen
  - Bacterial infection
  - Cardiac arrest
  - DS
- AE leading to death: 4 (4%)
  - 2 DS
  - 1 infection
  - 1 sudden death

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1. Komzifti (ziftomenib) [prescribing information]. San Diego, CA: Kura Oncology Inc; November 2025.
2. Wang ES, Montesinos P, Foran J, et al. Ziftomenib in relapsed or refractory NPM1-mutated AML. *Journal of Clinical Oncology,* 2025; 43(31): 3381-90.

Revumenib Patient Case

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Patient Case 1

- JP is a 63-year-old male with AML diagnosed November 2024. Cytogenetics remarkable for KMT2A-r. No significant past medical history. Current weight = 68 kg.
- Treatment course
  - 7+3 induction – resulted in CR
  - HiDAC consolidation – 3 cycles completed
  - Allogeneic HCT 5/7/25 from matched unrelated donor
  - Relapse 9/15/25 with extramedullary disease; KMT2A-r present
  - Plan to start revumenib
- Current Medications

Generic Name	Dose, Route, Frequency	Indication
Acetaminophen	500-1000 mg PO q6h PRN	Mild pain, headache
Acyclovir	800 mg PO BID	Viral prophylaxis
Dapsone	100 mg PO daily	Pneumocystis prophylaxis
Prochlorperazine	10 mg PO 4 times daily PRN	Nausea or vomiting

Revumenib Checklist

Dosing	
Patient weight	Patients ≥ 40 kg: 270 mg (160 mg tablet + 110 mg tablet) by mouth twice daily
Drug interactions	Concomitant strong CYP3A4 inhibitor: 160 mg by mouth twice daily
Baseline Monitoring	
Verify KMT2A-r or NPM1m	FDA-authorized test or FDA-approved companion diagnostic
Blood counts	Reduce WBC to < 25 K/uL before initiation
Electrolytes	Correct hypokalemia, hypomagnesemia, and other abnormalities before initiation
Electrocardiogram (ECG)	QTcF ≤ 450 msec
Embryo-fetal toxicity	Pregnancy test in females of reproductive potential within 7 days of initiation
Follow-up Monitoring	
Blood counts	At least monthly; signs and symptoms of differentiation syndrome
Electrolytes	Keep potassium ≥ 4 mEq/L and magnesium ≥ 2 mg/dL
ECG	Weekly for the first 4 weeks, then at least monthly thereafter
Embryo-fetal toxicity	Use effective contraception during treatment and for 4 months after the last dose

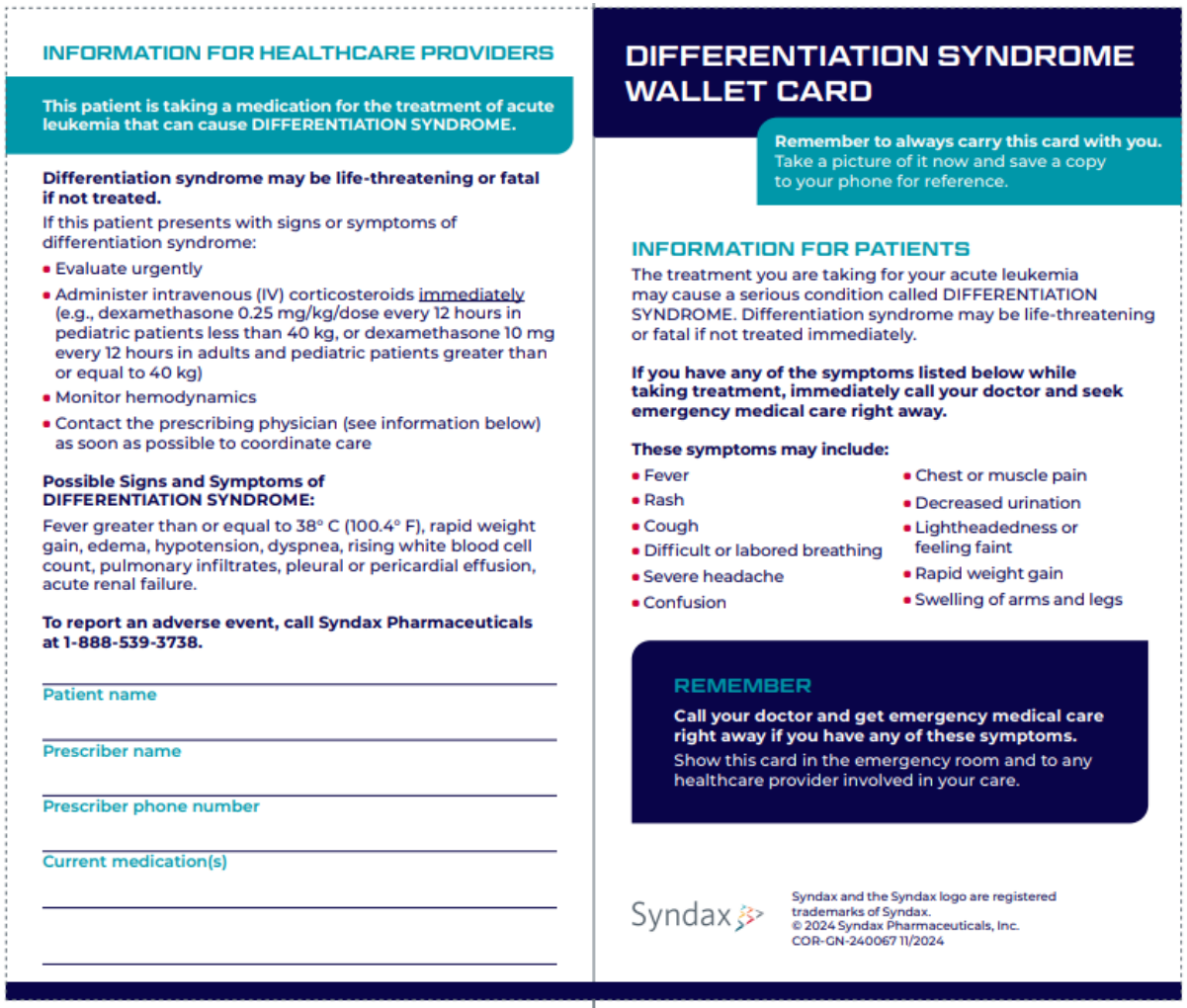
Revuforj (revumenib) [prescribing information]. New York, NY: Syndax Pharmaceuticals Inc; December 2025.

Patient Case 1

JP starts revumenib 270 mg PO BID. Two weeks later, he presents to clinic appointment with temperature of 101 ^{o}F, shortness of breath, and 5 kg weight gain. He is subsequently admitted.

WARNING: DIFFERENTIATION SYNDROME

Differentiation syndrome, which can be fatal, has occurred with REVUFORJ. Signs and symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, and renal dysfunction. If differentiation syndrome is suspected, immediately initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.



INFORMATION FOR HEALTHCARE PROVIDERS

This patient is taking a medication for the treatment of acute leukemia that can cause DIFFERENTIATION SYNDROME.

Differentiation syndrome may be life-threatening or fatal if not treated.

If this patient presents with signs or symptoms of differentiation syndrome:

- Evaluate urgently
- Administer intravenous (IV) corticosteroids immediately (e.g., dexamethasone 0.25 mg/kg/dose every 12 hours in pediatric patients less than 40 kg, or dexamethasone 10 mg every 12 hours in adults and pediatric patients greater than or equal to 40 kg)
- Monitor hemodynamics
- Contact the prescribing physician (see information below) as soon as possible to coordinate care

Possible Signs and Symptoms of DIFFERENTIATION SYNDROME:

Fever greater than or equal to 38° C (100.4° F), rapid weight gain, edema, hypotension, dyspnea, rising white blood cell count, pulmonary infiltrates, pleural or pericardial effusion, acute renal failure.

To report an adverse event, call Syndax Pharmaceuticals at 1-888-539-3738.

Patient name

Prescriber name

Prescriber phone number

Current medication(s)

DIFFERENTIATION SYNDROME WALLET CARD

Remember to always carry this card with you. Take a picture of it now and save a copy to your phone for reference.

INFORMATION FOR PATIENTS

The treatment you are taking for your acute leukemia may cause a serious condition called DIFFERENTIATION SYNDROME. Differentiation syndrome may be life-threatening or fatal if not treated immediately.

If you have any of the symptoms listed below while taking treatment, immediately call your doctor and seek emergency medical care right away.

These symptoms may include:

- Fever
- Rash
- Cough
- Difficult or labored breathing
- Severe headache
- Confusion
- Chest or muscle pain
- Decreased urination
- Lightheadedness or feeling faint
- Rapid weight gain
- Swelling of arms and legs

REMEMBER

Call your doctor and get emergency medical care right away if you have any of these symptoms.

Show this card in the emergency room and to any healthcare provider involved in your care.

Syndax

Froedtert ThedaCare

1. Revuforj (revumenib) [prescribing information]. New York, NY: Syndax Pharmaceuticals In
2. Revuforj wallet card. Available at: https://revuforjhcp.com/wp-content/uploads/2024/11/differentiation-syndrome-wallet-card.pdf?v=1771434220.

Revumenib DS

- Among all acute leukemia patients studied, DS occurred in 60 / 241 (25%)
  - Median time to initial onset: 9 days (range 3-41)
  - Some patients experienced more than 1 DS event
  - Revumenib interrupted in 7% of patients and discontinued in 1%
- Signs/symptoms
  - Fever
  - Dyspnea
  - Hypoxia
  - Rash
  - Hypotension
  - Peripheral edema
  - Pleural or pericardial effusion
  - Acute renal failure
  - Increasing WBC
- Management
  - Immediately start systemic corticosteroid (dexamethasone 10 mg IV q12h in adults) for at least 3 days until resolution of signs/symptoms
  - Interrupt revumenib if severe signs/symptoms persist for > 48 hours after starting corticosteroids, or earlier if life-threatening symptoms occur (i.e. pulmonary symptoms requiring ventilator support)
  - Restart corticosteroids promptly if DS recurs following taper

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Revuforj (revumenib) [prescribing information]. New York, NY: Syndax Pharmaceuticals Inc; December 2025.

Patient Case 1

- JP is started on dexamethasone 10 mg IV q12h for suspected DS. His symptoms improve over the next week, and he is discharged on a steroid taper. He has labs drawn once a week for electrolyte monitoring, and he completes weekly ECGs.
- He presents to clinic two weeks later with revumenib-related AEs
  - Nausea: no vomiting, not taking anti-emetic - trial prochlorperazine
  - Magnesium: trending 1.7-1.8 - initiate over-the-counter oral replacement
  - Potassium: trending 3.6-3.8 - initiate potassium PO 20 mEq daily
  - Diarrhea: 3-5 bowel movements per day most days, normally not loose – monitor
  - QTcF: 466 msec
- He presents to clinic one month later
  - Nausea: improved with addition of prochlorperaz
  - Magnesium: trending 1.8-2.1 - continue magnes
  - Potassium: trending 4-4.2 - continue potassium
  - Diarrhea: stable to slightly improved - monitor
  - QTcF: 485 msec
  - Peripheral blast count < 5%

WARNING: QTc PROLONGATION and TORSADES DE POINTES

QTc prolongation and Torsades de Pointes have occurred in patients receiving REVUFORJ. Correct hypokalemia and hypomagnesemia prior to and during treatment. Do not initiate REVUFORJ in patients with QTcF > 450 msec. If QTc interval prolongation occurs, interrupt, reduce, or permanently discontinue REFUVORJ.

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Revuforj (revumenib) [prescribing information]. New York, NY: Syndax Pharmaceuticals Inc; December 2025.

Revumenib QTc Prolongation

- Among all acute leukemia patients studied, QTc prolongation occurred in 86 / 241 (36%)
  - Grade 3 occurred in 15% of patients, and Grade 4 in 2%
  - QTcF > 500 msec in 10%
  - QTcF increase of > 60 msec from baseline in 24%
  - One patient died from cardiac arrest, and one patient had sustained Torsades de Pointes (TdP)
- Management
  - Correct electrolyte abnormalities
  - Complete ECG at baseline, weekly for the first 4 weeks, then monthly thereafter
    - More frequent ECG monitoring may be necessary in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or who are taking additional QTc-prolonging medications

QTcF Result	Action
481 – 500 msec	• Interrupt revumenib • Restart revumenib at same dose level once QTcF returns to ≤ 480 msec
> 500 msec	• Interrupt revumenib • Restart revumenib at reduced dose level once QTcF returns to ≤ 480 msec
Signs/symptoms of life-threatening arrhythmia, TdP, polymorphic ventricular tachycardia	Permanently discontinue revumenib

Revuforj (revumenib) [prescribing information]. New York, NY: Syndax Pharmaceuticals Inc; December 2025.

Patient Case 1

- JP's revumenib is held. Follow up ECG one week later shows improved QTcF of 443 msec and continued stable magnesium and potassium. Revumenib is resumed at the same dose of 270 mg PO BID.
- It has been approximately 4 months since JP started revumenib. He is still in remission and continues recommended monitoring.

Ziftomenib Patient Case

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Patient Case 2

- CC is a 54-year-old female with AML diagnosed May 2025. Cytogenetics remarkable for NPM1m. No significant past medical history. Current weight = 83 kg.
- Treatment course
  - Induction therapy on a clinical trial with an investigational agent + azacitidine + venetoclax – 4 cycles completed, then had disease progression
  - FLAG-Ida-Ven (fludarabine, cytarabine, filgrastim, idarubicin, venetoclax) – 1 cycle completed, resulting in reduction in blast percentage but persistent AML
  - Plan to start ziftomenib
- Current Medications

Generic Name	Dose, Route, Frequency	Indication
Acyclovir	800 mg PO BID	Viral prophylaxis
Famotidine	10 mg PO BID PRN	Acid reflux
Levofloxacin	500 mg PO daily	Bacterial prophylaxis
Posaconazole	300 mg PO daily	Fungal prophylaxis
Prochlorperazine	10 mg PO 4 times daily PRN	Nausea or vomiting
Sulfamethoxazole / trimethoprim	400 / 80 mg PO daily	Pneumocystis prophylaxis

Ziftomenib Checklist

Dosing	
Patient weight	Same for all patients: 600 mg PO once daily
Drug interactions	Take ziftomenib either 2 hours before or 10 hours after H2RA
Baseline Monitoring	
Verify NPM1m	Lab test via NGS or PCR
Blood counts	Reduce WBC to < 25 K/uL before initiation
Electrolytes	Correct hypokalemia and hypomagnesemia before initiation
ECG	QTcF ≤ 480 msec
Follow-up Monitoring	
ECG	Weekly for the first 4 weeks, then at least monthly thereafter
Embryo-fetal toxicity	Use effective contraception during treatment • Females of reproductive potential: and for 6 months after the last dose • Males with female partners of reproductive potential: and for 3 months after the last dose

Abbreviations not previously defined:
- NGS: Next-Generation sequencing
- PCR: Polymerase chain reaction

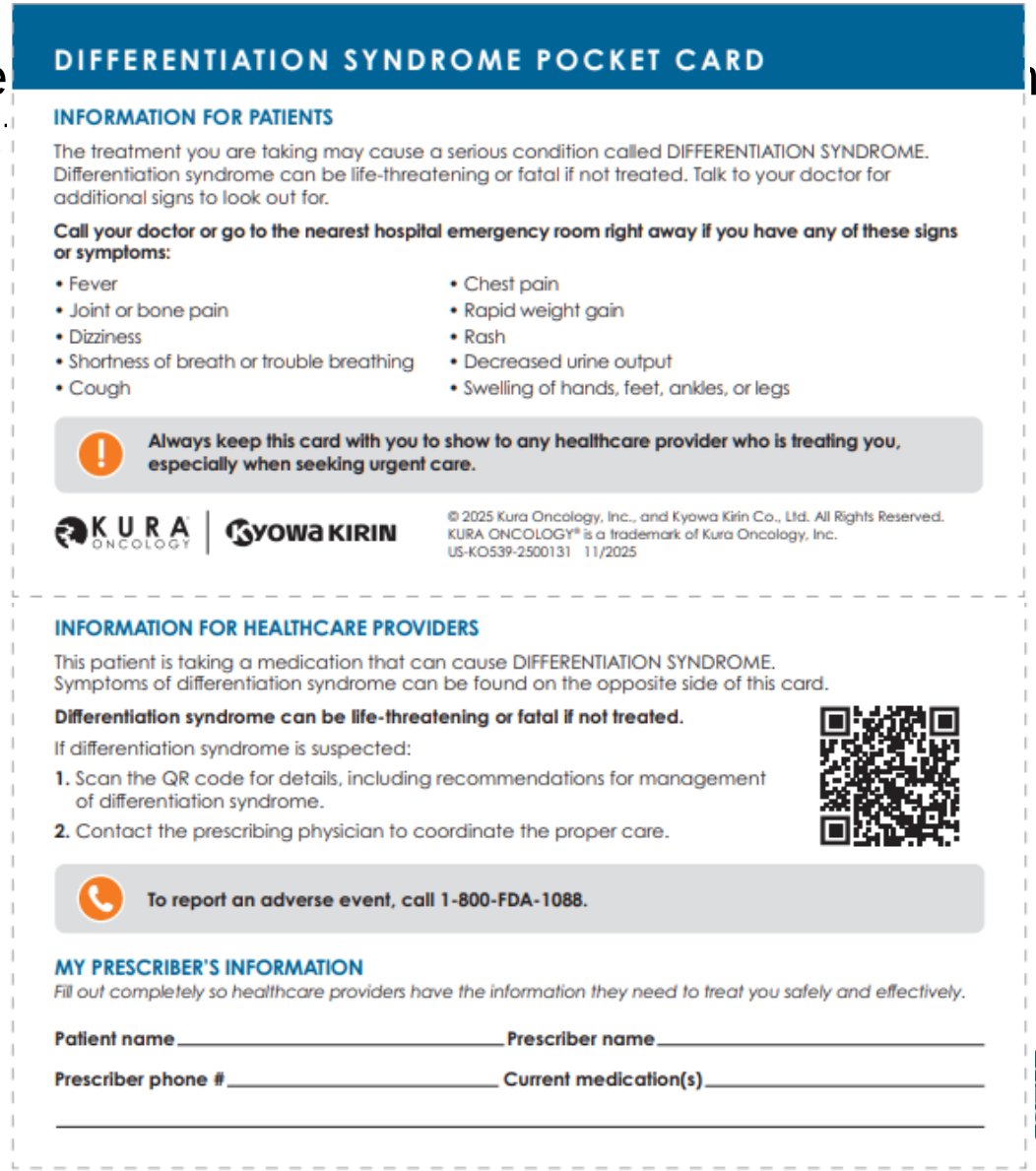
1. Komzifti (ziftomenib) [prescribing information]. San Diego, CA: Kura Oncology Inc; November 2025.
2. NPM1 testing flashcard. Available at: https://www.komziftihcp.com/files/resources-support/testing-flashcard.pdf.

Patient Case 2

CC starts ziftomenib 600 mg PO daily. Three wee…nia (101.7 °F) with chest pain, decreased urine outpu…

WARNING: 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 rashers. If differentiation syndrome is suspected, interrupt KOMZIFTI and initiate oral or intravenous corticosteroids with hemodynamic and laboratory monitoring until symptom resolution; resume KOMZIFTI upon symptom improvement.



DIFFERENTIATION SYNDROME POCKET CARD

INFORMATION FOR PATIENTS

The treatment you are taking may cause a serious condition called DIFFERENTIATION SYNDROME. Differentiation syndrome can be life-threatening or fatal if not treated. Talk to your doctor for additional signs to look out for.

Call your doctor or go to the nearest hospital emergency room right away if you have any of these signs or symptoms:

- Fever
- Joint or bone pain
- Dizziness
- Shortness of breath or trouble breathing
- Cough
- Chest pain
- Rapid weight gain
- Rash
- Decreased urine output
- Swelling of hands, feet, ankles, or legs

Always keep this card with you to show to any healthcare provider who is treating you, especially when seeking urgent care.

KURA ONCOLOGY | Kyowa Kirin

INFORMATION FOR HEALTHCARE PROVIDERS

This patient is taking a medication that can cause DIFFERENTIATION SYNDROME.
Symptoms of differentiation syndrome can be found on the opposite side of this card.

Differentiation syndrome can be life-threatening or fatal if not treated.

If differentiation syndrome is suspected:

1. Scan the QR code for details, including recommendations for management of differentiation syndrome.
2. Contact the prescribing physician to coordinate the proper care.

To report an adverse event, call 1-800-FDA-1088.

MY PRESCRIBER'S INFORMATION

Fill out completely so healthcare providers have the information they need to treat you safely and effectively.

Patient name _____ **Prescriber name** _____

Prescriber phone # _____ **Current medication(s)** _____

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1. Komzifti (ziftomenib) [prescribing information]. San Diego, CA: Kura Oncology Inc; November 2025.
2. Komzifti wallet card. Available at: https://www.komziftihcp.com/files/resources-support/pocket-guide.pdf.

Ziftomenib DS

- DS occurred in 29 / 112 (26%) NPM1m+ R/R AML patients
  - Median time to initial onset: 15 days (range 3-46)
  - Two patients experienced more than 1 DS event
  - Ziftomenib interrupted in 13% of patients and discontinued in 2%
  - Fatal DS occurred in 2 patients
- Management
  - Interrupt ziftomenib
  - Immediately start systemic corticosteroid (dexamethasone 10 mg PO or IV q12h in adults) for at least 3 days until resolution of signs/symptoms
  - Resume ziftomenib at same dose level when signs/symptoms improve and are ≤ Grade 2
  - Taper corticosteroid over a minimum of 3 days

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Komzifti (ziftomenib) [prescribing information]. San Diego, CA: Kura Oncology Inc; November 2025.

Patient Case 2

- CC's ziftomenib is held and she is started on dexamethasone 10 mg IV q12h for suspected DS. Her symptoms and labs improve, and she is discharged one week later on a steroid taper and resumed ziftomenib 600 mg PO daily. She has labs drawn three times a week for electrolyte monitoring and transfusion assessment.
- She presents to clinic two weeks later with ziftomenib-related AEs
  - Nausea: not taking anti-emetic – trial prochlorperazine
  - Itching: start loratadine
  - QTcF: 435 msec
- She presents to clinic one month later
  - Nausea: improved with prochlorperazine – continue to monitor
  - Itching: improved – continue to monitor
  - QTcF: 477 msec
  - Peripheral blast count < 5 %

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Komzifti (ziftomenib) [prescribing information]. San Diego, CA: Kura Oncology Inc; November 2025.

Ziftomenib QTc Prolongation

- QTc prolongation occurred in 13 / 112 (12%) R/R NPM1m+ AML patients
  - Grade 3 occurred in 8% of patients
  - QTcF > 500 msec in 9%
  - QTcF increase of > 60 msec from baseline in 12%
- Management
  - Correct electrolyte abnormalities
  - Complete ECG at baseline, weekly for the first 4 weeks, then at least monthly thereafter
    - More frequent ECG monitoring may be necessary in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or who are taking additional QTc-prolonging medications
  - Interrupt ziftomenib for QTcF > 500 msec or increase > 60 msec from baseline

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Komzifti (ziftomenib) [prescribing information]. San Diego, CA: Kura Oncology Inc; November 2025.

Patient Case 2

- CC continues on ziftomenib. She has few low-grade adverse effects, which remain tolerable. She does not have significant QTc prolongation, and her DS does not recur.
- Approximately 5 months into treatment with ziftomenib, CC's peripheral blast count increases to 43%. Bone marrow biopsy results with AML and 54% blasts. Plan to switch treatment to a clinical trial.

	Revumenib (Revuforj®)	Ziftomenib (Komzifti®)
Indication	• R/R acute leukemia in adult and pediatric patients with KMT2A-r • R/R AML in adult and pediatric patients with NPM1m	R/R AML in adult patients with NPM1m
Starting Dose	• Patients ≥ 40 kg: 270 mg (160 mg tablet + 110 mg tablet) PO twice daily • Patients < 40 kg: 160 mg/m^2 PO twice daily	600 mg (3 x 200 mg capsules) PO once daily
Food Impact	Take on an empty stomach, at least 1 hour before or 2 hours after a meal ***OR*** Take with a low-fat meal (~400 calories and ≤ 25% fat)	Take on an empty stomach, at least 1 hour before or 2 hours after a meal
DDIs	Concomitant strong CYP3A4 inhibitor: • Patients ≥ 40 kg: 160 mg PO twice daily • Patients < 40 kg: 95 mg/m^2 PO twice daily	• Avoid PPIs • Take ziftomenib either 2 hours before or 10 hours after H2RA • Take ziftomenib either 2 hours before or 2 hours after antacid
DS	**Black Box Warning –** Occurred in 25% of patients overall • Median time to onset: 9 days (range 3-41) • Treatment interruption in 7% of patients, discontinued in 1% Management • Reduce WBC to < 25 K/uL before starting revumenib • Monitor for signs/symptoms of DS • Administer systemic corticosteroid and hemodynamic monitoring for at least 3 days until symptom resolution o Adults ≥ 40 kg: dexamethasone 10 mg IV q12h o Pediatric patients < 40 kg: dexamethasone 0.25 mg/kg IV q12h • Hold revumenib if severe signs/symptoms for > 48 hours after starting corticosteroids	**Black Box Warning –** Occurred in 26% of NPM1m+ R/R AML patients • Median time to onset: 15 days (range 3-46) • Treatment interruption in 13% of patients, discontinued in 2%, two fatalities Management • Reduce WBC to < 25 K/uL before starting ziftomenib • Monitor for signs/symptoms of DS • **HOLD ziftomenib if DS suspected** • Administer systemic corticosteroid (dexamethasone 10 mg IV or PO q12h) and hemodynamic monitoring for at least 3 days until symptom resolution • Taper corticosteroid over at least 3 days
QTc Prolongation	**Black Box Warning –** Occurred in 36% of patients overall • Grade 3 occurred in 15% of patients, and Grade 4 in 2% • QTcF > 500 msec in 10%, QTcF increase > 60 msec in 24%, two fatalities Management • Correct electrolyte abnormalities • ECG at baseline, weekly x 4 weeks, then at least monthly • Interrupt revumenib if QTcF > 480 msec	Occurred in 12% of NPM1m+ R/R AML patients • Grade 3 occurred in 8% of patients • QTcF > 500 msec in 9%, QTcF increase > 60 msec in 12% Management • Correct electrolyte abnormalities • ECG at baseline, weekly x 4 weeks, then at least monthly • Interrupt ziftomenib if QTcF > 500 msec or increases > 60 msec from baseline
Electrolytes	Keep magnesium > 2 and potassium > 4 • If K 3.6-3.9 or Mg 1.7-1.9: supplement, continue revumenib • If K < 3.6 or Mg < 1.7: supplement, recheck next day. If K > 3.5 and/or Mg > 1.6, continue revumenib. If not, hold revumenib (can restart when correction complete)	Correct hypokalemia and/or hypomagnesemia before starting ziftomenib
Other AE	• Common: nausea (48%), diarrhea (29%), constipation (20%), hemorrhage (48%), infection without identified pathogen (46%), bacterial infection (27%), viral infection (23%), febrile neutropenia (37%), musculoskeletal pain (37%), fatigue (24%), edema (24%) • Serious (76% of patients overall): infection (29%), febrile neutropenia (20%), bacterial infection (15%), DS (13%), hemorrhage (11%)	• Common: diarrhea (36%), nausea (35%), hemorrhage (38%), infection without identified pathogen (52%), bacterial infection (28%), fatigue (34%), edema (30%), musculoskeletal pain (28%), pruritus (23%), febrile neutropenia (22%), increased transaminases (21%) • Serious (79% of patients overall): infection (29%), febrile neutropenia (18%), bacterial infection (16%), DS (16%), dyspnea (6%)

Future Directions / Pipeline

- Revumenib
  - AUGMENT-102 (with chemotherapy in R/R acute leukemias with KMT2A-r or amplification, NPM1m, or NUP98-r)
  - SAVE (with venetoclax and decitabine/cedazuridine [Inqovi®] in R/R AML and frontline AML)
  - NCT06222580 (with gilteritinib in FLT3+ R/R KMT2A-r or NPM1m AML)
  - Beat AML Master Trial (with azacitidine and venetoclax in frontline KMT2A-r or NPM1m AML)
  - SNDX-5613-0708 (with intensive chemotherapy in frontline KMT2A-r, NPM1m, or NUP98-r AML)
- Ziftomenib
  - KOMET-007 (with either azacitidine and venetoclax or 7 + 3 in newly diagnosed or R/R NPM1m or KMT2A-r AML)
  - KOMET-008 (with chemotherapy or with gilteritinib [if FLT3+] in R/R KMT2A-r or NPM1m AML)
- Pipeline
  - Bleximenib (JNJ-75276617)
  - Enzomenib (DSP-5336)
  - BMF-219
  - BN104

Froedtert ThedaCare

1. Joshi U, Shallis RM. Menin inhibition in acute myeloid leukemia: pathobiology, progress and promise. *Biomedicines,* 2026; 14(1): 219.
2. Thomas X. Small molecule menin inhibitors: novel therapeutic agents targeting acute myeloid leukemia with KMT2A rearrangement or NPM1 mutation. *Oncol Ther*, 2024; 12: 57-72.
3. Nadiminti KVG, Sahasrabudhe KD, Hongtao L. Menin inhibitors for the treatment of acute myeloid leukemia: challenges and opportunities ahead. *J Hematol Oncol*, 2024; 17: 113.
4. Canichella M, Papayannidis C, Mazzone C, de Fabritiis P. Therapeutic implications of menin inhibitors in the treatment of acute leukemia: a critical review. *Diseases,* 2025; 13: 227.
5. Isidori A, Marconi G. The role of menin inhibitors in acute myeloid leukemia. *Curr Opin Oncol,* 2025; 37(6): 641-9.

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Conclusions

- There are currently two FDA-approved menin inhibitors for the treatment of different relapsed or refractory acute leukemias
- Menin inhibitors have clinically meaningful response rates in patients with no other treatment options, but require frequent monitoring and follow-up for adverse effect management
- Anticipate additional menin inhibitors and combinations with menin inhibitors will be reviewed by FDA and approved

Questions?

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March 7, 2026

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