

Ziftomenib vs Revumenib in NPM1-Mutant AML

Clinical Data, Safety, and the Emerging Role of Menin Inhibition

Thomas Bokinz, PharmD

PGY2 Adult Oncology Pharmacy Resident

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Disclosures

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Learning Objectives

1. Describe the mechanism of action and clinical rationale for menin inhibition in NPM1-mutant acute myeloid leukemia (AML)
2. Assess clinical trial efficacy, safety, and key pharmacy considerations for revumenib and ziftomenib in NPM1-mutant AML

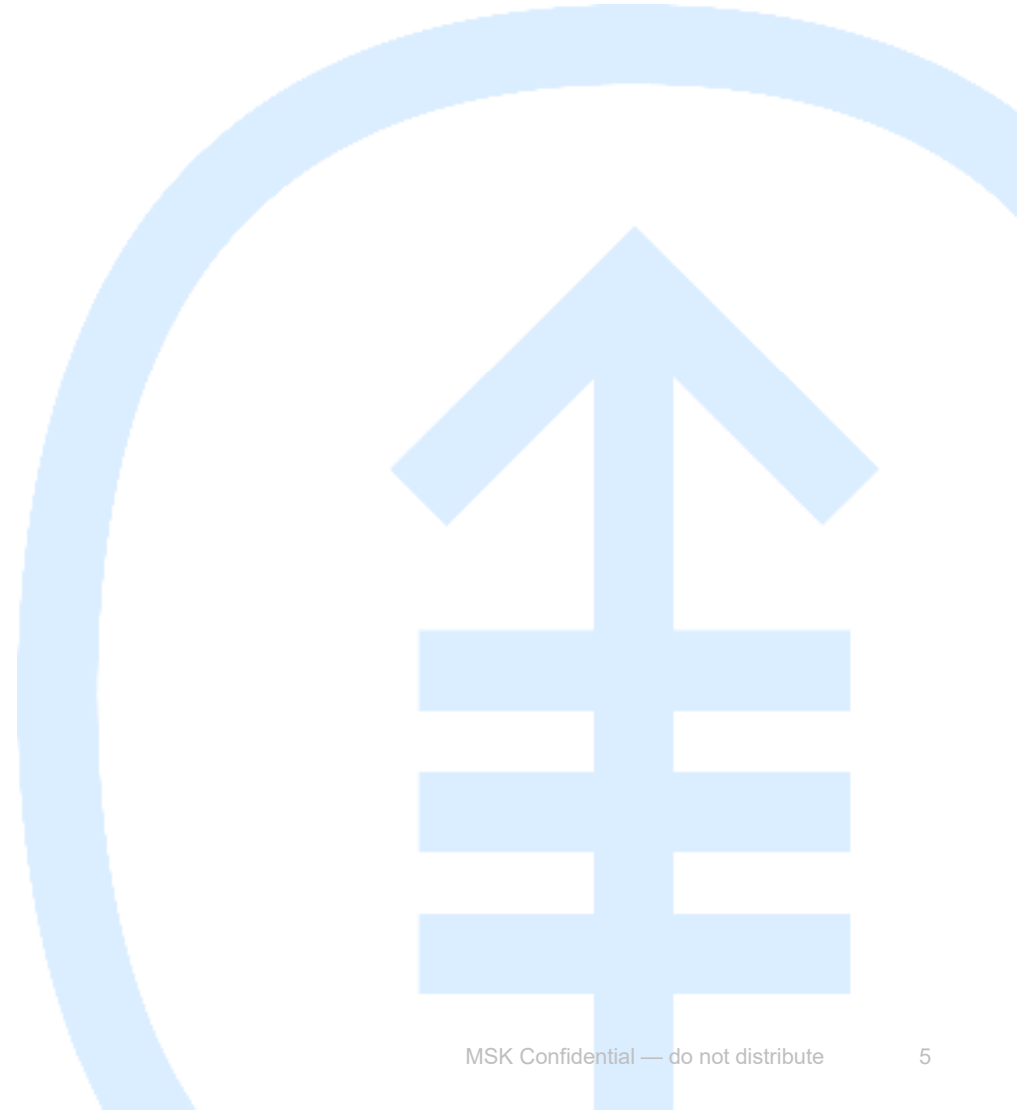
Definitions

Response	Morphologic Remission	Peripheral Blood Counts
Complete Remission (CR)	<ul style="list-style-type: none"> <5% blasts in the bone marrow Absence of circulating blasts or extramedullary disease Transfusion independence 	ANC $\geq 1.0 \times 10^9/L$ <u>AND</u> PLTs $\geq 100 \times 10^9/L$
CR with Partial Hematologic Recovery (CRh)		ANC $\geq 0.5 \times 10^9/L$ <u>AND</u> PLTs $\geq 50 \times 10^9/L$
CR with Incomplete Hematologic Recovery (CRi)		ANC $< 1.0 \times 10^9/L$ <u>OR</u> PLTs $< 100 \times 10^9/L$
Morphologic Leukemia-Free State (MLFS)	Same as above without requirement for transfusion independence	N/A

Composite Complete Remission (CRc)

- Combined CR + CRh + CRi

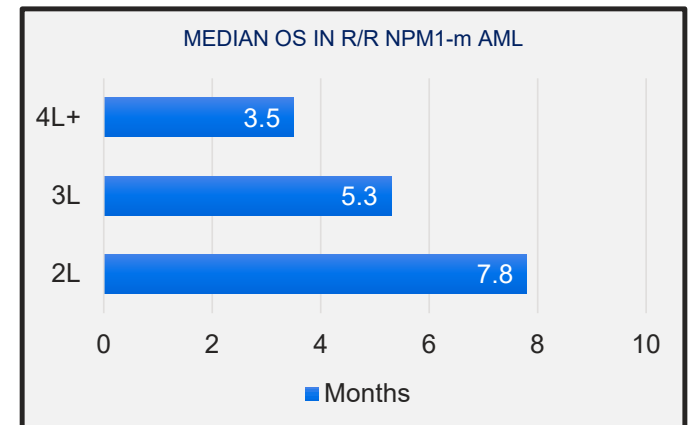
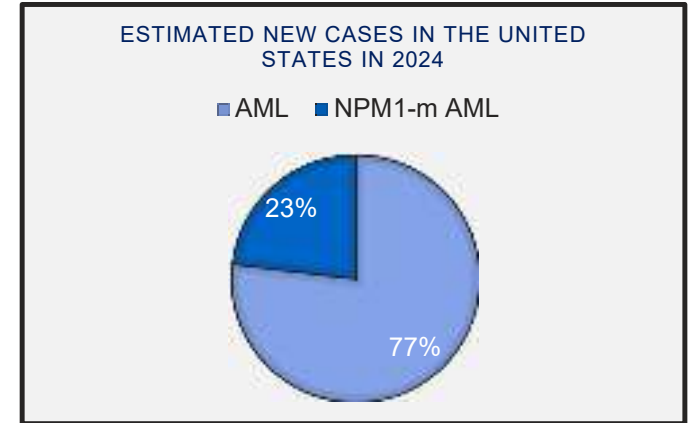
Background



Nucleophosmin 1 Mutations (NPM1)

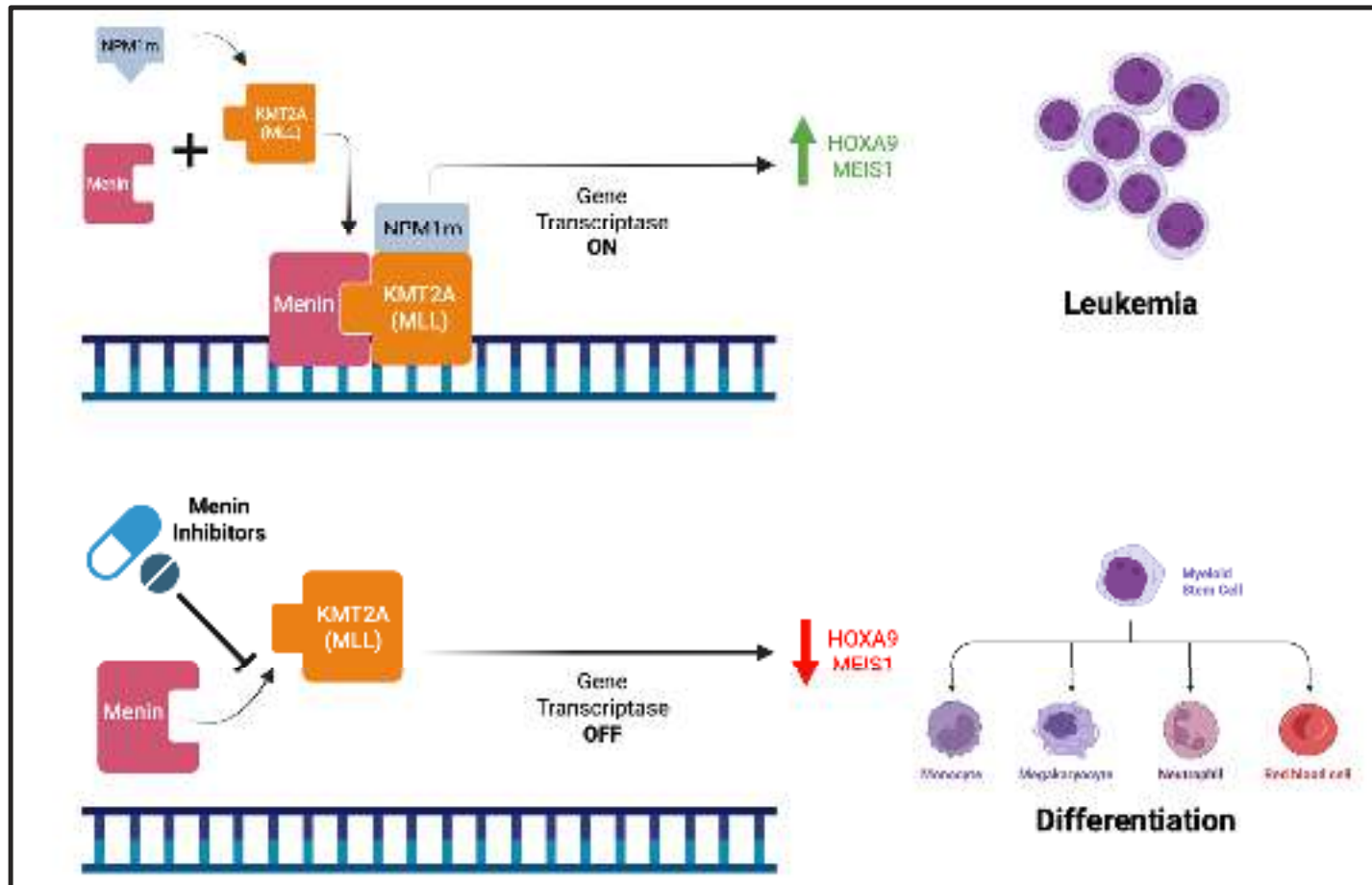
- Occur in 28-35% of cases of AML
- Commonly occurring co-mutations:
 - **FLT3-ITD 40%**
 - IDH1/2 15-30%
 - DNMT3A 50%
- Associated with favorable outcomes in the frontline setting except in:
 - Older age
 - Relapse/Refractory Disease

Risk Category	Genetic Abnormality
Favorable	Mutated NPM1 without FLT3-ITD
Intermediate	Mutated NPM1 with FLT3-ITD
Poor/Adverse	Mutated NPM1 with adverse-risk cytogenetics



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Pathophysiology



AUGMENT-101 Trial

Arellano ML, et al. (2025)

Menin inhibition with revumenib for NPM1-mutated relapsed or refractory acute myeloid leukemia	
Design & Population	<ul style="list-style-type: none"> Global, multicenter, open-label, phase II study Relapsed or refractory NPM1-m AML (N=64 in efficacy cohort & 84 in safety cohort)
Intervention	<ul style="list-style-type: none"> Revumenib 270 mg PO Q12 (160 mg/m² if <40 kg) continuously in 28-day cycles <ul style="list-style-type: none"> 160 mg PO Q12 <u>with</u> strong CYP3A4 inhibitors (95 mg/m² if <40 kg)
Results	<ul style="list-style-type: none"> Primary Endpoint: CR/CRh 23.4% (p=0.0014) <ul style="list-style-type: none"> Median time to CR/CRh: 2.76 months Median duration of CR/CRh: 4.7 months <u>Other secondary endpoints:</u> <ul style="list-style-type: none"> Median time to first response: 1.84 months Median OS: 4 months Median OS among CR/CRh: 23.3 months Grade ≥3 AEs of interest: QTc prolongation 21.4% & differentiation syndrome 13.1% <ul style="list-style-type: none"> Discontinuations due to adverse effects: 4.8%
Conclusion	Revumenib demonstrated clinical activity in R/R NPM1-m AML population

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KOMET-001 Trial

Wang ES, et al. (2025)

Ziftomenib in Relapsed or Refractory NPM1-Mutated AML	
Design & Population	<ul style="list-style-type: none"> • Global, multicenter, open-label, registrational-enabling, phase II study • Relapsed or refractory NPM1-m AML (N=92)
Intervention	<ul style="list-style-type: none"> • Ziftomenib 600 mg PO once daily continuously in 28-day cycles
Results	<ul style="list-style-type: none"> • Primary Endpoint: CR/CRh 22% (p=0.0058) <ul style="list-style-type: none"> ○ Median time to CR/CRh: 2.8 months ○ Median duration of CR/CRh: 3.7 months ○ MRD negativity among CR/CRh: 61% • <u>Other secondary endpoints:</u> <ul style="list-style-type: none"> ○ Median time to first overall response 1.9 months ○ Median OS: 6.6 months ○ Median OS among responders: 18.4 months ○ Transfusion independence conversion 20% & maintenance 20% • Grade ≥3 AEs of interest: QTc prolongation 3% & differentiation syndrome 15% <ul style="list-style-type: none"> ○ Discontinuations due to adverse effects: 3%
Conclusion	Ziftomenib demonstrated clinical activity in R/R NPM1-m AML population

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Comparing Menin Inhibitors

Trial	AUGMENT-101	KOMET-001
Baseline Characteristics	Median 65 years old (≥65 years old 51.6%) FLT3-ITD 34.4% IDH1/2-m 25% Previous venetoclax 75% Previous HSCT 21.9% Previous FLT3-inhibitor 46.9% Previous IDH1/2-inhibitor 11% RAS mutant 3.1% TP53 mutant 6.3%	Median 69 years old (≥65 years old 64%) FLT3-ITD 45% IDH1/2-m 33% Previous venetoclax 59% Previous HSCT 24%
Efficacy	23.4% achieved CR/CRh Median time to CR/CRh: 2.76 months Median duration of CR/CRh: 4.7 months MRD- : Not reported for NPM1 cohort	22% achieved CR/CRh Median time to CR/CRh: 2.8 months Median duration of CR/CRh: 3.7 months MRD- : 61%
Adverse Effects	<u>Grade ≥3:</u> Anemia 14.3% Febrile Neutropenia 13.1% Decreased Platelets 10.7% Differentiation Syndrome 13.1% QTc Prolongation 21.4%	<u>Grade ≥3:</u> Anemia 5% Neutropenia 7% Differentiation Syndrome 15% QTc Prolongation 3%

Critique

AUGMENT-101		KOMET-001	
Strengths	Limitations	Strengths	Limitations
<ul style="list-style-type: none"> • Evaluated TP53 & RAS mutations • Evaluated HOXA9 expression as a biomarker 	<ul style="list-style-type: none"> • Did not report MRD 	<ul style="list-style-type: none"> • Evaluated transfusion independence • MEN1 mutation activity 	<ul style="list-style-type: none"> • Allowed DS prophylaxis in high-risk patients & did not report usage • Did not report prior targeted therapies

Clinical Application



Clinical Pearls & Considerations

	Revumenib	Ziftomenib
Formulation	Oral Tablet	Oral Capsule
Dosing & Administration	270 mg PO Q12 continuously in 28-day cycles fasted or low-fat meal (400 calories, ≤25% fat)	600 mg PO once daily continuously in 28-day cycles on an empty stomach
Black Box Warnings	<ul style="list-style-type: none"> Differentiation Syndrome QTc Prolongation and TdP 	<ul style="list-style-type: none"> Differentiation Syndrome
Drug Interactions	<ul style="list-style-type: none"> Major CYP3A4 Substrate (adjust for strong inhibitors) 	<ul style="list-style-type: none"> Major CYP3A4 Substrate (no adjustment for inhibitors) PPIs, H2RAs* & antacids*
Dose Adjustments	<ul style="list-style-type: none"> Weight <40 kg No renal or hepatic dose adjustments 	<ul style="list-style-type: none"> No renal or hepatic dose adjustments
QTc Prolongation Management	<ul style="list-style-type: none"> Do not initiate if QTc >450 msec QTc >480-500 msec = Hold & resume same dose QTc >500 msec or >60 msec increase from baseline = Hold until ≤480 msec & reduce dose 	<ul style="list-style-type: none"> Do not initiate if QTc >480 msec QTc >480-500 msec = Continue QTc >500 msec or >60 msec increase from baseline = Hold until ≤480 msec & resume same dose
Differentiation Syndrome Management	<ul style="list-style-type: none"> Suspected? = Continue & give systemic steroids Severe >48 hours or life-threatening = Hold & resume same dose once ≤ grade 1 	<ul style="list-style-type: none"> Suspected? = Hold & give systemic steroids Severe >48 hours or life-threatening = Hold & resume same dose once ≤ grade 2

Assessment Question

History of Present Illness:

BP is 64-year-old male with relapsed AML harboring an NPM1 mutation presenting after progression on azacitidine plus venetoclax. The patient was recently hospitalized for an upper GI bleed and has since started twice-daily pantoprazole. Baseline ECG demonstrates a QTc of 423 msec. Medication review reveals concomitant posaconazole therapy for antifungal prophylaxis.

1. Which of the following is most appropriate when selecting between menin inhibitors?

- A. Choose revumenib 270 mg PO every 12 hours as it can be administered concomitantly with PPIs
- B. Choose ziftomenib 200 mg PO once daily as it can be administered concomitantly with PPIs
- C. Choose revumenib 160 mg PO every 12 hours as it can be administered concomitantly with PPIs
- D. Choose ziftomenib 600 mg PO once daily as it can be administered concomitantly with PPIs



Conclusion

- ☑ Currently, there are two FDA-approved menin inhibitors for relapsed or refractory NPM1 mutant AML
- ☑ Selection between menin inhibitors should be guided by patient specific factors such as QTc risk, adherence, and drug-drug interactions
- ☑ Management of menin inhibitor adverse effects varies between agents, and pharmacists should be aware of these key differences when optimizing patient care

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