COMPARATIVE TOXICITY OF MENIN INHIBITOR-BASED COMBINATION THERAPY IN NEWLY DIAGNOSED AML: VENETOCLAX-CONTAINING VERSUS NON-VENETOCLAX REGIMENS

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BACKGROUND

NPM1-mutated and KMT2A-rearranged AML depend on menin-KMT2A driven HOX/MEIS transcription. Menin inhibition disrupts this program and promotes differentiation.[6]

Menin inhibitors are being studied with venetoclax plus a hypomethylating agent (HMA) or intensive 7+3 in clinically different populations; comparative toxicity evidence remains limited.

Understanding comparative safety signals can support anticipatory monitoring and patient counseling.

OBJECTIVE

To compare reported safety outcomes across venetoclax-containing and 7+3 menin-inhibitor regimens using an exploratory, indirect cross-trial analysis not a head-to-head or causal comparison.

METHODS

- Structured review of peer-reviewed trials, official ASH/EHA reports, and ClinicalTrials.gov through May 2026.
- Study-level aggregate safety data were analyzed using each endpoint's reported denominator; NR was not treated as zero.
- Two-sided Fisher's exact tests generated p values. ORs and 95% CIs were calculated from 2×2 tables; a 0.5 Haldane Anscombe correction addressed zero-event tables.
- An exact conditional sensitivity analysis assessed zero-event differentiation-syndrome comparisons. No randomization, matching, or confounder adjustment was performed.

KEY RESULT

25.6% vs **47.1%**

Grade ≥3 febrile neutropenia

BEAT AML 11/43 vs KOMET-007 7+3 24/51 • OR 0.39 (95% CI 0.16–0.93)

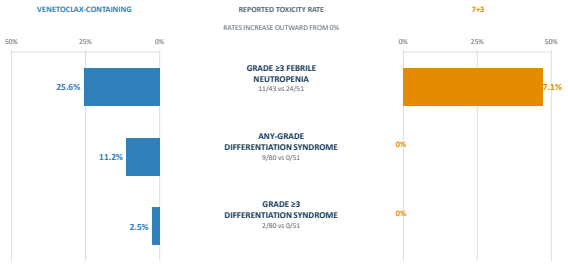
- Severe differentiation syndrome was uncommon: 2/80 (2.5%) vs 0/51 (0%); Haldane Anscombe corrected Wald (HA-Wald) OR 3.28 (95% CI 0.15-69.73).
- Any-grade differentiation syndrome: 9/80 (11.2%) vs 0/51 (0%); HA-Wald OR 13.69 (95% CI 0.78–240.49). Fisher's exact p = 0.012 and the corrected CI differ because they use different estimators; exact sensitivity 95% CI 1.34–.
- QTc prolongation, cytopenias, discontinuation, and early mortality could not be compared because the corresponding 7+3 outcomes were NR.

TABLE 1. COHORT CONTEXT AND REPORTED TOXICITIES

COMPARISON	VENETOCLAX-CONTAINING		7+3 BACKBONE
COHORT CONTEXT Population differs across cohorts	**BEAT AML[1,2]** Rev + Ven/Aza n=43 • median age: 73 y* • unfit	**KOMET-007[3,5]** Zift + Ven/Aza n=37 • median age: 75 y* • fitness status NR	**KOMET-007[4,5]** Zift + 7+3 n=51 • median age: 59 y* • fit
REPORTED TOXICITIES — n/N (%)			
Differentiation syndrome Any grade	8/43 (19%)	1/37 (3%)	0/51 (0%)
Differentiation syndrome Grade ≥3	2/43 (5%)	0/37 (0%)	0/51 (0%)
QTc prolongation Grade 3	5/43 (12%)	1/37 (3%)	NR
Febrile neutropenia Grade ≥3 • principal comparison	**11/43 (25.6%)**	NR	**24/51 (47.1%)**
Early mortality Definition NR/unverified	3/43 (7%)	4/37 (11%)	NR

Schedules: BEAT AML-Rev D1-28, Aza D1-7, Ven D1-28; KOMET-007 7+3-Zift 600 mg QD from D8; Zift + Ven/Aza schedule: NR.
NR = not reported. *Median ages not independently confirmed. Data cutoffs, CTCAE versions, mortality definitions and causes, and a common KOMET-007 cutoff were not verifiable in accessible official records.
Blue/orange emphasis identifies the principal Grade ≥3 febrile-neutropenia comparison; cross-trial populations are not exchangeable.

FIGURE 1. REPORTED TOXICITY RATES (%)



GRADE ≥3 FEBRILE NEUTROPENIA: 25.6% vs 47.1% | OR 0.39 (95% CI 0.16–0.93)

Blue = venetoclax-containing cohorts; orange = 7+3. Endpoint denominators differ.
CROSS-TRIAL CAUTION: unadjusted populations differed in age, fitness, treatment intensity, follow-up, and adverse-event reporting.

CONCLUSION

- In this indirect cross-trial comparison, Grade ≥3 febrile neutropenia was reported less often in BEAT AML than in the KOMET-007 7+3 cohort (25.6% vs 47.1%; OR 0.39, 95% CI 0.16–0.93). This exploratory association does not establish that the regimen backbone caused the difference.
- Severe differentiation syndrome was uncommon. The any-grade estimate remained highly imprecise because the 7+3 cohort had no reported events.
- These hypothesis-generating findings warrant prospective confirmation using harmonized safety definitions.

CLINICAL SIGNIFICANCE

- Monitor for differentiation syndrome, QTc prolongation, cytopenias, infections (including febrile neutropenia), treatment discontinuation, and early mortality according to the regimen and applicable labeling.
- Between-cohort differences and incomplete reporting preclude claims of superiority or treatment recommendations. Prospective comparisons with harmonized safety definitions are needed.

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