Current Treatment Patterns and Safety Outcomes in Relapsed/Refractory Acute Myeloid Leukemia With an *NPM1* Mutation: A Systematic Literature Review

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Introduction & Objective

Evolving R/R *NPM1*-m AML landscape

- Relapsed/refractory (R/R) acute myeloid leukemia (AML) with a *nucleophosmin 1* mutation (*NPM1*-m), present in approximately 30% of AML cases, remains difficult to treat and is associated with a poor prognosis.[1-3]
- In 2025, the Food and Drug Administration (FDA) approved revumenib and ziftomenib for patients with R/R AML with susceptible *NPM1*-m who have no satisfactory alternative treatment options,[4-6] creating a need to contextualize use and tolerability of historical treatments as mutation-directed care reshapes treatment pathways.
- Before 2025, treatment largely relied on approaches that did not directly target menin–*lysine [K]-specific methyltransferase 2A* (*KMT2A*)-dependent disease biology.[7]
- Treatment options included salvage chemotherapy, venetoclax-based regimens, FMS-like tyrosine kinase 3 (FLT3)- or isocitrate dehydrogenase 1/2 (IDH1/2)-directed therapy when actionable, and allogeneic hematopoietic stem cell transplantation (HSCT) for eligible patients.[8]

OBJECTIVE:
To characterize the treatment patterns and safety outcomes in adults with R/R *NPM1*-m AML during the period preceding approval of menin inhibitors.

Methods

Eligibility, screening, and data extraction

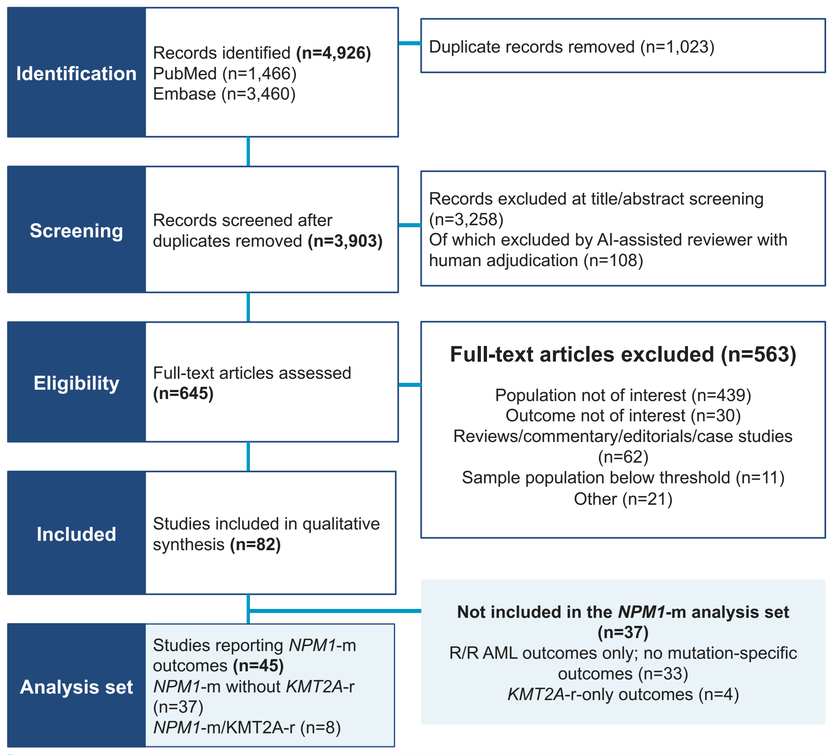
- A systematic literature review (SLR) was conducted per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[9] using PubMed and Embase searches of peer-reviewed, English-language publications from January 2019 through December 2024.
- Eligible studies reported outcomes related to treatment, treatment patterns, safety, and adverse events in R/R AML with *NPM1*-m or *KMT2A*-rearrangement (*KMT2A*-r); this analysis focuses on *NPM1*-m.
- PubMed and Embase searches identified 4,926 records; 3,903 unique records were screened after duplicate removal.
- Title/abstract screening used one human and one artificial intelligence (AI)-assisted reviewer with human adjudication; two independent human reviewers assessed full texts and extracted study characteristics and safety outcomes.
- Studies reporting *NPM1*-m outcomes formed the primary analysis set; the broader qualitative synthesis retained all included studies.

Table 1. Eligibility Criteria for the *NPM1*-m Analysis

PICOS Element	Criteria
Population	Adults with R/R AML harboring an *NPM1*-m
Intervention	Any pharmacologic treatment or cellular therapy
Comparator	Any or none
Outcomes	Outcomes related to treatment, treatment patterns, safety and adverse events
Study design	Clinical trials and prospective or retrospective observational studies
Database Limits	Available abstracts, English language only
Temporal Limits	Original research or abstract 2019-2024; conference abstracts 2022-2024

PRISMA flow and the 45-study analysis subset

Figure 1. PRISMA Flow and Derivation of the 45-Study *NPM1*-m Analysis Set



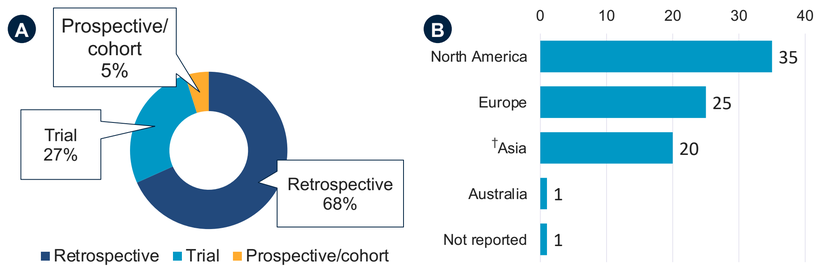
The 82-study synthesis covered both *NPM1*-m and *KMT2A*-r evidence; all subsequent results focus on the 45 studies reporting *NPM1*-m outcomes.

Results

82-study qualitative synthesis: study characteristics and geographic distribution

- Of 645 full-text articles assessed, 82 studies met the inclusion criteria and were included in the broader qualitative synthesis.
- Most were retrospective (68%, n=56) or clinical trials (27%, n=22); 5% (n=4) were prospective/cohort studies (Figure 2A).
- Studies were primarily conducted in North America (n=35), Europe (n=25), and Asia (n=20) (Figure 2B).
- Forty-five of the 82 studies reported *NPM1*-m outcomes and formed the primary analysis set: 34 *NPM1*-m only, 3 *NPM1*-m with co-mutations, and 8 reported both *NPM1*-m and *KMT2A*-r populations.

Figure 2. Distribution of Included Studies by (A) Study Design and (B) Geographic Region (N=82)



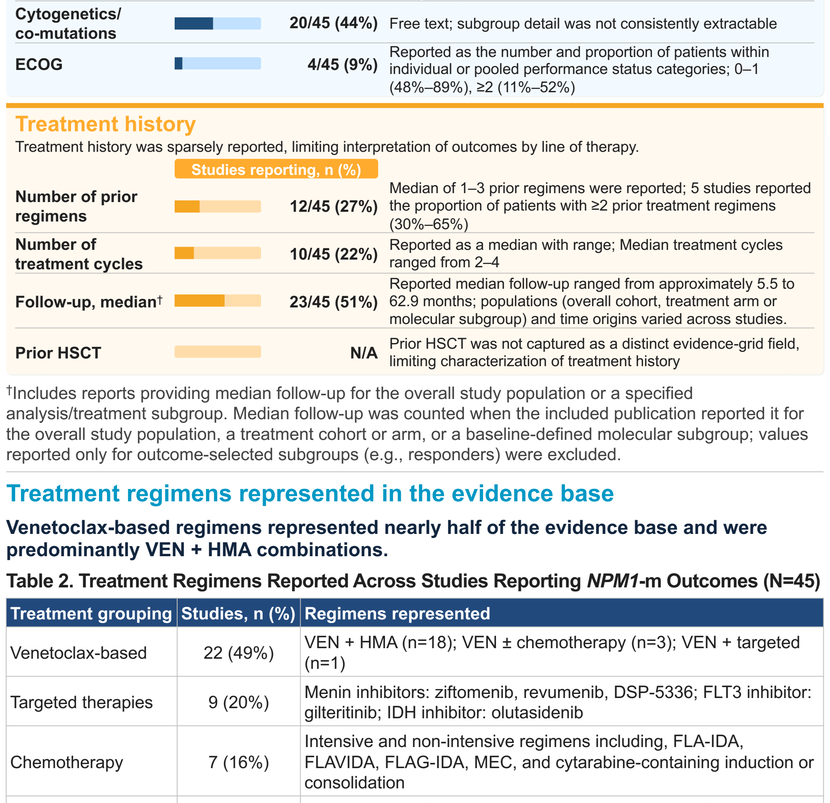
† Asia (n=20) includes countries in the Middle East

PRIMARY EVIDENCE FOCUS: Subsequent results will cover the 45 studies reporting *NPM1*-m outcomes

45-study *NPM1*-m analysis set

Reporting of key patient and disease characteristics was inconsistent, with notable gaps in treatment history, disease risk characterization, and performance status.

Figure 3. Availability and Reporting of Key Characteristics Across Studies Reporting *NPM1*-m Outcomes (N=45)



†Includes reports providing median follow-up for the overall study population or a specified analysis/treatment subgroup. Median follow-up was counted when the included publication reported it for the overall study population, a treatment cohort or arm, or a baseline-defined molecular subgroup; values reported only for outcome-selected subgroups (e.g., responders) were excluded.

Treatment regimens represented in the evidence base

Venetoclax-based regimens represented nearly half of the evidence base and were predominantly VEN + HMA combinations.

Table 2. Treatment Regimens Reported Across Studies Reporting *NPM1*-m Outcomes (N=45)

Treatment grouping	Studies, n (%)	Regimens represented
Venetoclax-based	22 (49%)	VEN + HMA (n=18); VEN ± chemotherapy (n=3); VEN + targeted (n=1)
Targeted therapies	9 (20%)	Menin inhibitors: ziftomenib, revumenib, DSP-5336; FLT3 inhibitor: gilteritinib; IDH inhibitor: olutasidenib
Chemotherapy	7 (16%)	Intensive and non-intensive regimens including, FLA-IDA, FLAVIDA, FLAG-IDA, MEC, and cytarabine-containing induction or consolidation
Cellular therapies	4 (9%)	Allogeneic HSCT; second cellular therapy, including DLI or second allogeneic HSCT
Other/unspecified†	4 (9%)	Multiple/pooled treatments; unspecified treatment; prognostic/molecular study

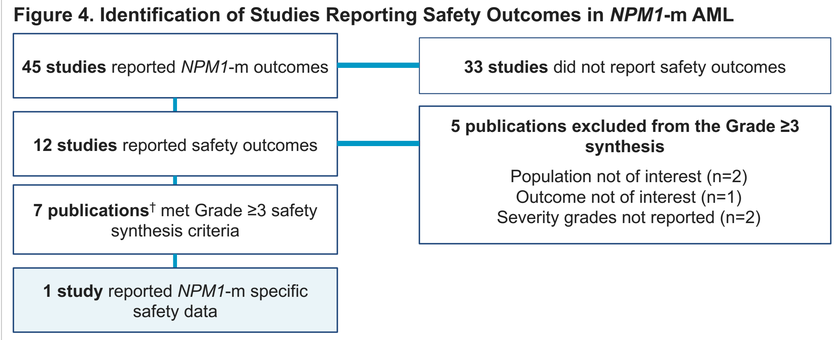
† Other/unspecified included studies with heterogeneous or pooled treatment approaches, studies for which outcomes could not be attributed to a single specified treatment grouping, and one prognostic/molecular study without a specified treatment regimen.

- Categories are not mutually exclusive. One study (Issa 2023) contributed to both venetoclax-based and targeted groupings.
- Cellular therapy studies are shown for completeness and excluded from the pharmacologic safety analysis.

Safety-evidence availability and selection

Nearly three-quarters of studies reporting NPM1-m outcomes did not report safety outcomes; 7 publications met criteria for the Grade ≥ 3 synthesis.

Figure 4. Identification of Studies Reporting Safety Outcomes in *NPM1*-m AML



† Seven qualifying publications represented six unique studies/trials; Erba 2023 and Wang 2024 are separate reports from KOMET-001.

Safety evidence across studies

Safety evidence varied across study designs, treatment regimens, and AE grading conventions (Table 3).

Table 3. Characteristics of Studies Reporting Safety Outcomes (N=12)

Study	Design	Treatment grouping	Population as reported	AE grades
Angotzi 2024	Retrospective	Venetoclax + HMA	R/R AML	Grades 1–2 and ≥3
Daver 2023	Clinical trial	Targeted: DSP-5336	R/R Acute leukemia (23 AML; 1 ambiguous lineage)	Grades 1–2 and ≥3†
Erba 2023	Clinical trial	Targeted: ziftomenib	R/R AML with *NPM1*-m	Any grade and ≥3
Huang 2023	Retrospective	Venetoclax + HMA	AML (8/31 R/R)	Baseline Grade ≥3 cytopenias‡
Issa 2023	Clinical trial	Revumenib + VEN + ASTX727	R/R AML/MPAL (adults and children)	Any grade and ≥3§
Labrador 2022	Retrospective	Venetoclax-based	R/R AML	Grade 3/4 collected; AE grades NR¶
Petit 2024	Retrospective	Venetoclax + HMA	R/R AML	Any grade and Grade 3-4
Piccini 2021	Retrospective	Venetoclax-based	R/R AML	Grades 2-4 and hematologic AEs ≥3/4
Shahswar 2024	Retrospective	Chemotherapy: FLA-IDA/ FLAVIDA	R/R AML	Any grade and Grade 3/4
Todisco 2023	Retrospective	Venetoclax + HMA	R/R AML	Any grade and ≥3
Wang 2024	Clinical trial	Targeted: ziftomenib	R/R AML	Grades 1–2 and ≥3
Yu 2023	Prospective/ cohort	Venetoclax + azacitidine ± HHT	R/R AML	AE grades NR††

† Daver 2023 is excluded from the adult severe-adverse event (AE) synthesis as trial included R/R AML, ALL or acute leukemia of ambiguous lineage; ‡ Huang 2023 is excluded from the adult severe-AE synthesis as safety outcomes include baseline cytopenias; § Issa 2023 is excluded from the adult severe-AE synthesis because safety data were pooled across adult and pediatric patients; ¶ Labrador 2022 is excluded from the adult severe-AE synthesis as severity grades for safety outcomes are not reported; †† Yu 2023 is excluded from the adult severe-AE synthesis as severity grades for safety outcomes are not reported.

Grade ≥3 adverse-event reporting

Hematologic events were the most frequently reported Grade ≥3 AEs, with rates ranging from 7% to 100% across studies (Table 4). One ziftomenib study (Erba 2023) reported NPM1-m specific Grade ≥3 safety outcomes for R/R AML patients.

Table 4. Grade ≥3 Adverse Events by Publication (n=7)

Adverse event†	Angotzi 2024 VEN + HMA N=44	Petit 2024 VEN + HMA N=35	Piccini 2021 VEN-based N=47	Todisco 2023 VEN + HMA (REF) N=68	Todisco 2023 VEN + HMA (REL) N=79	Shahswar 2024 FLA-IDA + VEN N=37	Erba 2023 Ziftomenib R/R AML with *NPM1*-m N=20	Wang 2024‡ Ziftomenib R/R AML; all molecular subtypes N=83
Neutropenia	42 (95.4%)	NR	47 (100%)	14 (20.6%)	21 (26.6%)	37 (100%)	NR	8 (9.6%)
Decreased neutrophil count	NR	NR	NR	NR	NR	NR	NR	6 (7.2%)
Thrombocytopenia	32 (72.7%)	NR	45 (95.7%)	11 (16.2%)	19 (24.1%)	37 (100%)	4 (20%)	11 (13.3%)
Decreased platelet count	NR	NR	NR	NR	NR	NR	NR	6 (7.2%)
Anemia	20 (45.5%)	NR	45 (95.7%)	6 (8.8%)	7 (8.9%)	37 (100%)	5 (25%)	20 (24.1%)
Febrile neutropenia	28 (63.6%)	NR	NR	11 (16.2%)	17 (21.5%)	36 (97.0%)	NR	18 (21.7%)
Sepsis	4 (9.1%)	NR	NR	2 (2.9%)	7 (8.9%)	4 (11.0%)	NR	10 (12.0%)
Pneumonia	2 (4.5%)	NR	NR	3 (4.4%)	8 (10.1%)	1 (3.0%)§	NR	16 (19.3%)
Differentiation syndrome	NR	NR	NR	NR	NR	NR	NR	12 (14.5%)
Infection	NR	18 (51.4%)	NR	NR	NR	NR	NR	NR
Cardiac toxicity	NR	NR	NR	1 (1.5%)	1 (1.3%)	NR	NR	NR
Liver toxicity	NR	NR	NR	0	1 (1.3%)	NR¶	NR	NR
Hypoxia	NR	NR	NR	NR	NR	NR	NR	7 (8.4%)
Diarrhea	NR	NR	NR	0	1 (1.3%)	NR	NR	4 (4.8%)
Nausea	NR	NR	NR	0	1 (1.3%)	NR	NR	NR
Digestive toxicity	NR	1 (2.9%)	NR	NR	NR	NR	NR	NR
Fatigue	2 (4.5%)	NR	NR	1 (1.5%)	0	NR	NR	3 (3.6%)

† Reported AEs are not exhaustive; the number and types of AEs reported varied across publications; ‡ Derived from mutually exclusive Grade 3-5 categories in Wang 2024 Table 2: Grade 3, n=32; Grade 4, n=21; Grade 5, n=23; § Grade 3/4 fungal pneumonia was reported separately (n=4, 11%); ¶ Reported Grade 3 elevated liver enzymes (n=4,11%); these were not classified as liver toxicity.

- Values are n (%) as reported in each source; populations and treatment regimens differ across studies; most studies reported broader R/R AML populations; NR indicates the event was not reported or not reported under that term in the source.
- Piccini 2021 reported 6 microbiologically defined Grade 3–4 infectious events (Grade 3, n=4; Grade 4, n=2); event-level data were not included in the table because patient-level incidence was not reported. Febrile neutropenia was reported in 21 patients (45%) without severity grading.
- Todisco 2023 reports two treatment cohorts, shown separately.
- Interpretation guardrail: Rates should not be compared across studies because designs, populations, denominators, and reporting conventions differed and no quantitative synthesis was performed.

Discussion

Published evidence reflected a broad range of treatment regimens and inconsistent safety reporting, limiting characterization of treatment patterns and comparative safety.

What the evidence supports

- Of the 45 studies reporting *NPM1*-m related outcomes, 37 reported *NPM1*-m and no *KMT2A*-r specific outcomes, and eight reported both *NPM1*-m and *KMT2A*-r specific outcomes.
- Within the 45-study *NPM1*-m analysis set, safety was reported in only 12 studies, with one ziftomenib study reporting *NPM1*-m-specific safety data; the remaining safety evidence was generally reported for broader R/R AML or combined molecular populations, limiting characterization of *NPM1*-m-specific safety.
- Venetoclax-based regimens were the most frequently represented treatment grouping (22/45), but study counts reflect the published evidence base rather than treatment utilization.
- The review provides a descriptive pre-approval baseline; post-approval evidence should reassess treatment pathways and report outcomes and safety by mutation status.

Limitations

- Population, treatment selection, dose, schedule, combination partners, and reporting conventions were heterogeneous.
- No quantitative synthesis or indirect comparison was performed. These findings do not estimate treatment utilization or support comparative safety conclusions.
- Prior HSCT was not captured as a distinct evidence-grid field.
- Searches were limited to English-language records identified in PubMed and Embase.

Conclusions

Pre-approval evidence provides a baseline but leaves important *NPM1*-m-specific evidence gaps

Safety data were reported in 12 of 45 studies, including one *NPM1*-m-specific safety report for ziftomenib.
Most treatment and safety evidence was reported for the broader R/R AML populations.

- **Interpret cautiously:** Heterogeneity in study design and reporting limits meaningful cross-study comparisons.
- **Generate *NPM1*-m evidence:** Future studies should report patient characteristics, treatment exposure, outcomes, and adverse events by mutation status.
- **Reassess the pathway:** Post-approval evidence should characterize treatment pathways and safety as mutation-directed therapies enter practice following the 2025 United States (US) approvals of revumenib and ziftomenib.

Evidence implication: These gaps underscore the need for continued *NPM1*-m-specific evidence generation to characterize patient characteristics, treatment exposure, outcomes, and safety as treatment pathways evolve in the post-approval setting.

Abbreviations: AE, adverse event; AI, artificial intelligence; ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; ASTX727, decitabine and cedazuridine; DLI, donor lymphocyte infusion; DSP-5336, Dainippon Sumitomo Pharma-5336 (enzomenib); ECOG, Eastern Cooperative Oncology Group scale; ELN, European LeukemiaNet; FDA, Food and Drug Administration; FLA-IDA, fludarabine, cytarabine, and idarubicin; FLAG-IDA, fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin; FLAVIDA, fludarabine, cytarabine, idarubicin, and venetoclax; FLT3, FMS-like tyrosine kinase 3; HHT, homoharringtonine; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplantation; IDH, isocitrate dehydrogenase; IDH1/2, isocitrate dehydrogenase 1/2; *KMT2A*, *lysine [K]-specific methyltransferase 2A*; *KMT2A*-r, *lysine [K]-specific methyltransferase 2A*-rearrangement; MEC, mitoxantrone, etoposide, and cytarabine; MPAL, mixed-phenotype-acute leukemia; N/A, not applicable; *NPM1*-m, *nucleophosmin 1* mutation; NR, not reported; PICOS, population, intervention, comparator, outcomes, and study design; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; REF, refractory; REL, relapsed; R/R, relapsed/refractory; SLR, systematic literature review; US, United States; VEN, venetoclax.

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AI platform disclosure: Nested Knowledge was used as the AI-enhanced platform to facilitate the SLR process.
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References: General and SLR references to be accessed via QR code.