

CPX-351 in secondary/high-risk acute myeloid leukemia: a meta-analysis of randomized and real-world studies encompassing more than 3,200 patients

Acute myeloid leukemia (AML) encompasses a biologically and clinically heterogeneous group of disorders. Among these, therapy-related AML (t-AML) and AML arising from antecedent myelodysplastic syndromes (MDS) or myeloproliferative neoplasms (MPN) are consistently associated with poorer prognosis. Contemporary classifications increasingly emphasize genetic and morphological criteria. The International Consensus Classification (ICC) prioritizes morphologic and molecular characteristics and subsequently applies the “therapy-related” qualifier (a complex clinical entity characterized by its association with prior exposure to cytotoxic agents or radiotherapy), whereas the 5th edition of the World Health Organization (WHO) classification replaces the former category of “AML with myelodysplasia-related changes (MRC)” with “AML, myelodysplasia-related (AML-MR).” AML-MR is defined by $\geq 20\%$ myeloid blasts in the presence of specific myelodysplasia-associated cytogenetic or molecular abnormalities and may arise *de novo* or following MDS/MDS-MPN.¹⁻³

CPX-351 is a liposomal co-formulation of cytarabine and daunorubicin at a fixed 5:1 molar ratio, engineered to deliver synergistic drug exposure directly to leukemic blasts.⁴ In a pivotal randomized phase III trial involving older adults with newly diagnosed high-risk or secondary AML, CPX-351 significantly improved overall survival (OS) compared to the conventional “7+3” regimen. Longer-term follow-up demonstrated a median OS of 9.56 months *versus* 5.95 months ($P=0.003$) favoring CPX-351, with sustained benefit observed in subsets eligible for allogeneic hematopoietic stem cell transplantation (allo-HSCT).^{5,6} These results have led to the broad integration of CPX-351 in clinical practice and spurred numerous real-world evidence (RWE) studies across diverse patient populations and healthcare settings. Nevertheless, a comprehensive synthesis comparing RWE outcomes with those from randomized controlled trials (RCT) - encompassing both efficacy and safety endpoints - is currently lacking in the literature.

To address the gap, we conducted a meta-analysis with two primary aims: (i) to synthesize outcomes for patients treated with CPX-351 across RCT and RWE cohorts, and (ii) to compare effect sizes between RCT and RWE studies for key endpoints - complete remission (CR), 1-year OS, rate of allo-HSCT post-response, and early mortality.

Following a prespecified protocol and adhering to PRISMA 2020 guidelines,⁷ we included RCT and observational RWE studies enrolling adults (≥ 18 years) with newly diagnosed AML receiving CPX-351 as single-agent induction therapy,

with or without consolidation according to study-specific protocols or routine care (*Online Supplementary Figure S1*). Studies assessing CPX-351 in combination regimens (e.g., with venetoclax or gemtuzumab ozogamicin),^{8,9} and those involving relapsed/refractory AML, were excluded. The study respects the ethical rules of the country in which it has been performed.

A systematic search of MEDLINE (PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov was conducted through December 2024, with no language or publication-status restrictions. Search terms included “acute myeloid leukemia,” “AML,” “CPX-351,” and “real-world.” Two independent reviewers performed study screening, data extraction, and quality assessment (MM and DG). Primary endpoints were CR, including CR with incomplete hematologic recovery (CRi) where consistently reported; 1-year OS; proportion of patients proceeding to allo-HSCT among responders or all treated patients, as specified; and 30- and 60-day mortality. Given anticipated clinical and methodological heterogeneity, random-effects models were applied for meta-analysis, with heterogeneity quantified using Q statistics and the I^2 index. Comparisons between RCT and RWE results were descriptive, based on subgroup-specific pooled estimates with corresponding confidence intervals.

We identified 16 eligible studies involving 3,280 patients treated with CPX-351. This included two RCT comparing CPX-351 *versus* standard cytarabine-daunorubicin (7+3) and *versus* FLAG-Ida, comprising 258 patients in CPX-351 arms.^{5,10} Fourteen were observational RWE cohorts from Europe and North America, representing 3,022 patients (list of RWE studies is available in the *Online Supplementary Appendix*). Median patient ages ranged from late 50s to late 60s, consistent with the target population of secondary/high-risk AML. Across all studies, consolidation treatment was delivered with CPX-351 at doses and schedules consistent with the approved product labeling. Diagnostic criteria varied across studies, encompassing t-AML, AML-MR/MRC, and “secondary AML,” with variation especially notable among RWE cohorts, which also included some younger adults (Table 1). Most of the studies were conducted prior to 2022; consequently, the diagnostic definitions of s-AML relied on earlier classification systems, preceding the current ICC and WHO 2022 classifications. However, the aforementioned limitation did not significantly impact the meta-analytic results.

The RCT population comprised the US/Canada pivotal

program (median age 67.8 years) and the UK NCRI AML19 high-risk cohort (median age 57 years). The RWE datasets included national registries (e.g., England's NCRAS, N=353; England CAS, N=602), multicenter consortia (e.g., MARROW, N=267; CREST-UK, N=147), and single- or multicenter institutional series from Germany, Italy (2 cohorts), France, Spain (2 cohorts), and US centers (N ranges, 59-513). Median age in RWE cohorts ranged between 60 and 67 years, broadly aligning with RCT demographics.

The pooled CR rate across all studies was 56% (95% confidence interval [CI]: 50-61%) with significant heterogeneity ($Q=82.46$; $P<0.001$; $I^2=85\%$). Notably, pooled CR rates were nearly identical between RCT (56%; 95% CI: 40-71%) and RWE (56%; 95% CI: 50-62%) ($P=0.23$) (Figure 1A). The overall pooled 1-year OS was 54% (95% CI: 51-57%), also with significant heterogeneity ($Q=51.19$; $P<0.001$; $I^2=71\%$). Notably, 1-year OS was lower in RCT (47%; 95% CI: 35-60%) compared to RWE cohorts (55%; 95% CI: 52-58%) ($P=0.13$) (Figure 1B). Among responders, 38% (95% CI: 33-43%) proceeded to allo-HSCT (the mean percentage of patients undergoing allo-HSCT in CR1 was 83% [95% CI: 75-100%]), with high variability ($Q=126.57$; $P<0.001$; $I^2=88\%$). RCT reported 41% (95% CI: 24-59%), and RWE cohorts 38% (95% CI: 32-43%) ($P=0.193$) (Figure 1C). Thirty-day mortality was uniformly 6% across all studies with moderate heterogeneity ($Q=12.44$; $P=0.13$; $I^2=36\%$) and was consistent between RCT and RWE (6%; 95% CI for RCT: 3-9%; RWE 5-8%; $P=0.587$) (Figure

1D). Sixty-day mortality, reported in nine studies, was 10% overall with higher heterogeneity ($Q=50.76$; $P<0.001$; $I^2=80\%$), but slightly higher in RCT (13%; 95% CI: 9-18%) versus RWE (9%; 95% CI: 6-13%; $P=0.03$) (Online Supplementary Figure S2; Table 2).

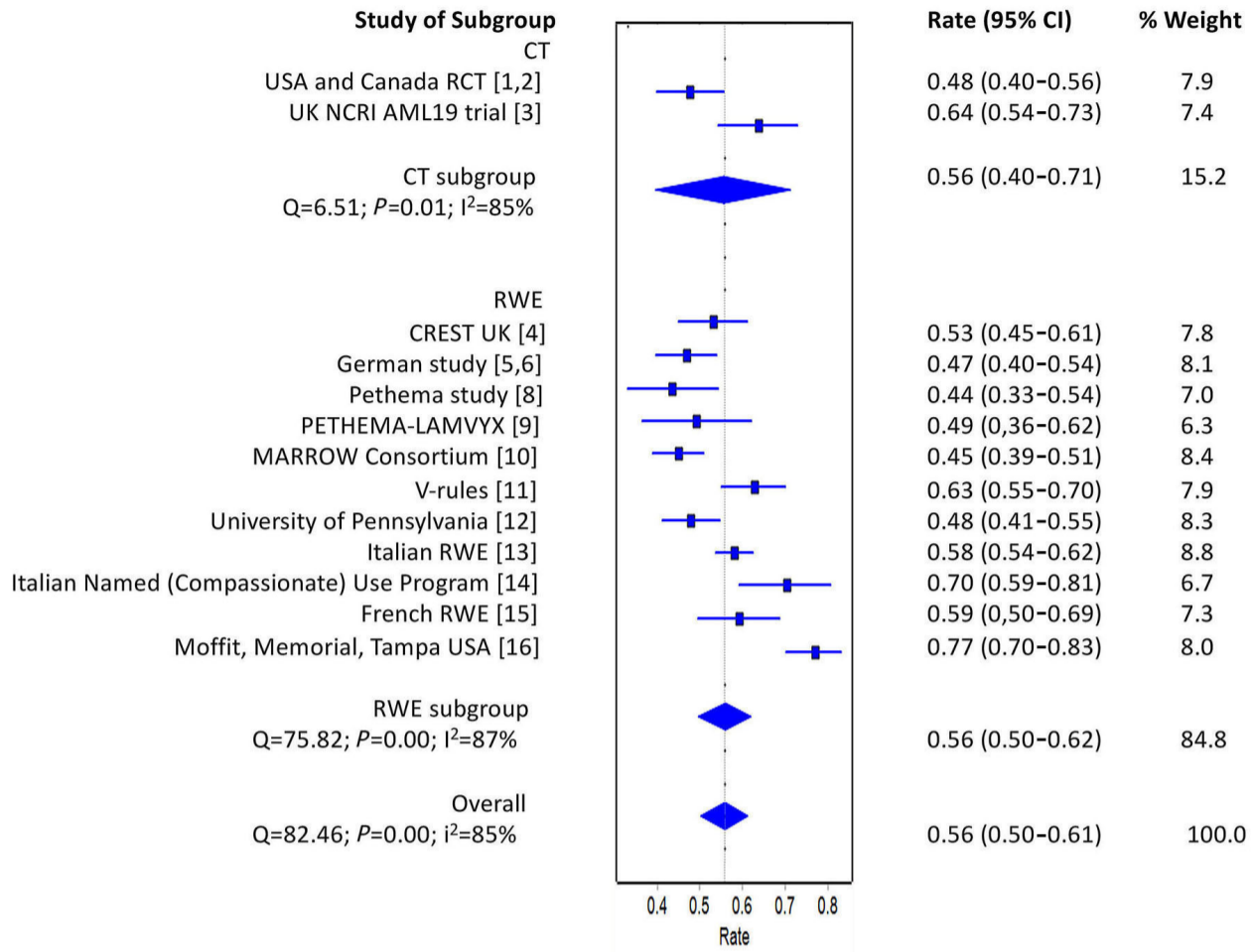
There are several aspects qualifying the results of this meta-analysis. Firstly, RWE did not underperform compared with RCT, contrary to common expectations. The pivotal phase III trial selectively enrolled older patients with uniformly high-risk disease and applied strict definition criteria for therapy-related and myelodysplasia-related AML, potentially enriching for adverse biology.⁵ In addition, RWE cohorts are heterogeneous, including younger adults, evolving diagnostic classifications (t-AML, AML-MR/MRC, secondary AML), and potentially benefiting from advances in supportive care and transplant practices over time. Also, the rate of patients accessing to an allo-HSCT procedure varied between the two RCT (approximately 33-50%), underscoring the impact of institutional policies and donor availability on survival beyond induction therapy.¹¹⁻¹³ Finally, differences in treatment delivery, including outpatient administration and earlier referral to transplant, may mitigate toxicity and improve bridging to curative approaches. Although substantial heterogeneity across studies is expected given geographic, temporal, and patient-selection diversity, the concordance of CR rates between RCT and RWE populations is reassuring, supporting the generaliz-

Table 1. Randomized controlled trials (RCTs) and real-world evidence (RWE) studies included in the meta-analysis.

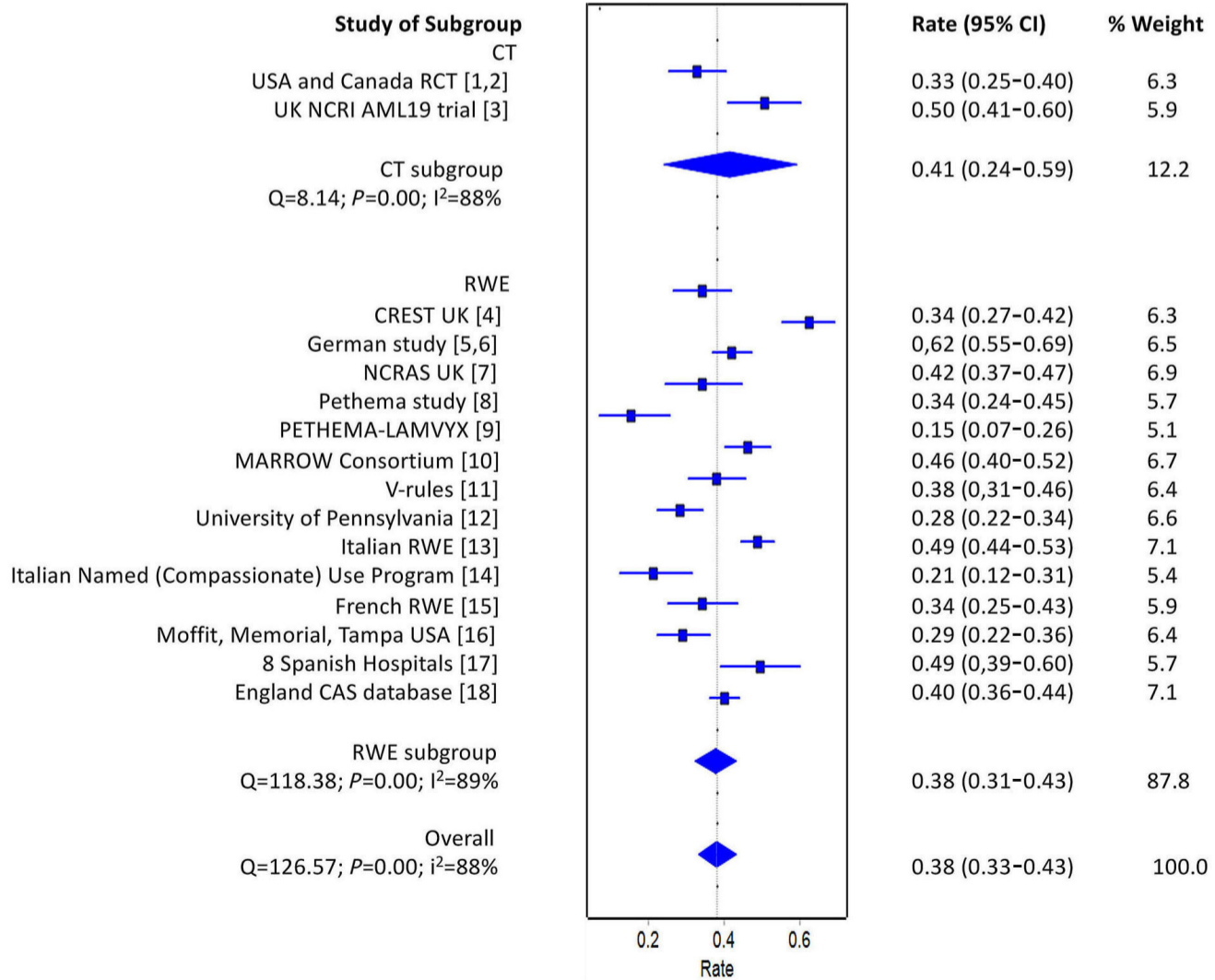
Study	Author (year)	N of pts	Males, %	Median age, years	TP53, %	Median OS, months (95% CI)
USA and Canada RCT	Lancet JE (2021)	153	61	67.8	-	9.33 (37-11.86)
UK NCRI AML19 trial	Othman J (2023)	105	67	57	45	13.3
CREST UK	Mehta P (2024)	147	64	64	26	12.8
German study	Rautenberg C (2021)	188	63	65	7/14*	21
NCRAS UK	Legg A (2023)	353	64	62	-	12.9
Pethema study	Bernal T (2023)	85	57	67	-	10.3
PETHEMA-LAMVYX	Rodríguez-Arbolí E (2025)	59	68	64	14	7.4 (3.7-12.7)
MARROW Consortium	Peters DT (2024)	267	-	63	17	15
V-rules	LeBlanc TW (2025)	161	-	60	25	12.9 (8.9-19.7)
University of Pennsylvania	Matthews AH (2022)	217	48	65	15	13
Italian RWE	Guolo F (2025)	513	51	65.6	14.6	16.23 (13.6-18.9)
Italian Named (Compassionate) Use Program	Guolo F (2020)	71	55	66	35	NR
French RWE	Chiche E (2021)	103	52	67	28	16.1 (range, 13.1-16.7)
Moffitt, Memorial, Tampa USA	Lee D (2022)	169	59	67	14	16
8 Spanish hospitals	Fernández Villalobos MJ (2024)	87	63	65	4/21*	-
England CAS database	Lambova A (2025)	602	63	63	-	12.8

*Data expressed as N/N and not as %. pts: patients; OS: overall survival; CI: confidence interval; NR: not reached.

A

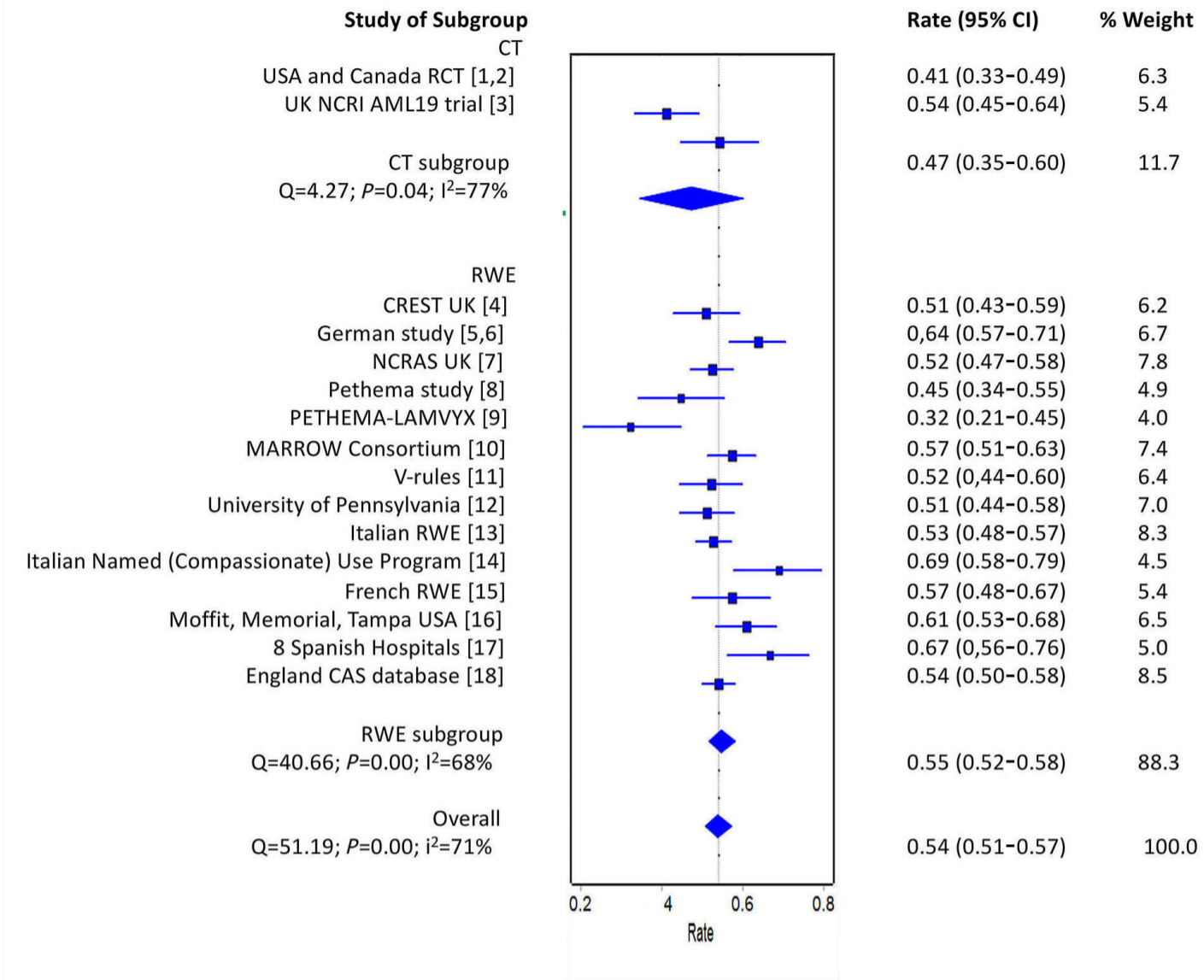


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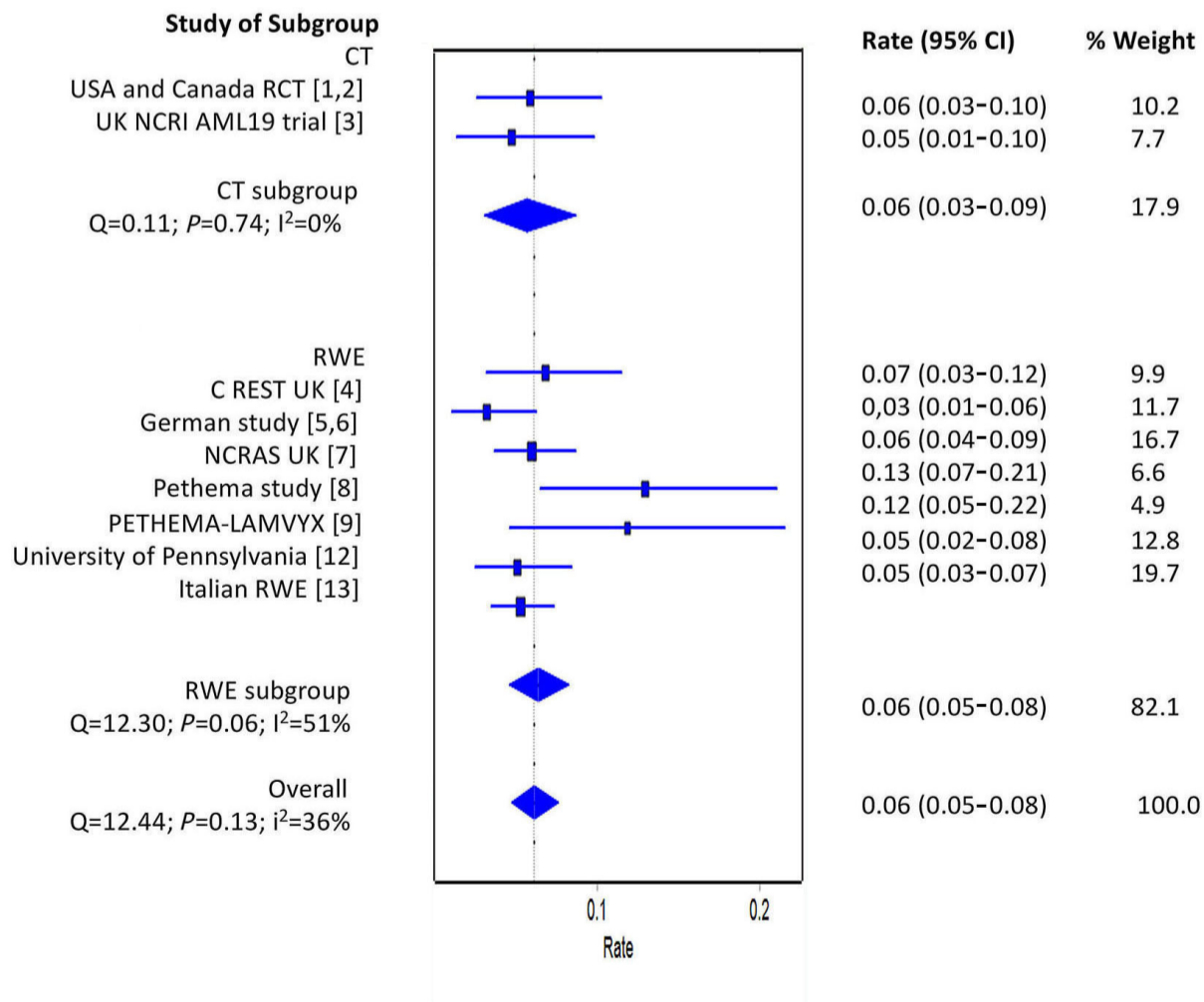


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Figure 1. Forest plot of the composite complete remission, the rate of allogeneic transplantation, the 1-year overall survival and the 30-days mortality from the studies included in this meta-analysis.

(A) Forest plot of the composite complete response (CR) from the studies included in this meta-analysis. In a forest-plot view, study-level CR estimates vary widely (reflecting differences in age, baseline risk, and transplant policies), yet the diamond-shaped pooled estimate for randomized controlled trials (RCT) overlaps closely with that for real-world evidence (RWE), visually underscoring the consistency of CR with CPX-351 across controlled and routine-practice settings. (B) Forest plot of the rate of allogeneic transplantation performed in patients from the included studies in this meta-analysis. The forest plot reveals substantial inter-study variation in transplant rates - driven by differences in fitness, donor availability, and national policies - yet the pooled estimates for RCT and RWE remain closely aligned, supporting the concept of CPX-351 as an effective “bridge-to-transplant” platform in both trial and practice. (C) Forest plot of the 1-year overall survival from the included studies in this meta-analysis. The forest plot indicates a rightward shift (higher survival proportions) in several large RWE datasets relative to the RCT. While confidence intervals partly overlap, the visual impression is that everyday practice yielded at least comparable - and in aggregate slightly higher - 1-year survival. (D) Forest plot of the 30-day mortality in patients from the included studies in this meta-analysis. The pooled estimate sits near 6% with narrow 95% confidence intervals (CI) across subgroups, visually conveying early safety consistency. RT: controlled trials.

ability of CPX-351’s disease-reducing efficacy. In addition, the stability of 30-day mortality at approximately 6% supports acceptable early safety in routine clinical practice. The observed lower 60-day mortality in RWE relative to RCT (8.5-9% vs. 12-13%, depending on the cohort) may reflect contemporary care pathways and an evolving learning curve in managing CPX-351-related toxicities. These patterns suggest that real-world settings may benefit from improved familiarity with CPX-351 and that early safety signals can be favorable outside trial environments.

Our findings complement prior meta-analytic work by Sandhu *et al.*,¹⁴ which reported an indirect comparison between cohorts treated exclusively with CPX-351 and those treated with the 3+7 regimen. Collectively, both analyses support CPX-351 as a consolidated benchmark for future studies testing novel agents in the context of secondary/high-risk AML. This is particularly relevant for patients with AML-MR and t-AML, in whom CPX-351 demonstrates robust remission induction that facilitates allo-HSCT.

Early mortality rates with CPX-351 are comparable to, and survival outcomes are at least equivalent to, those observed with intensive chemotherapy, and may be superior in real-world settings. These findings endorse the sustained preferential use of CPX-351 in eligible patients and underscore the importance of optimizing transplant referral and timing after induction. Emerging data on dosing strategies and peri-transplant integration in real-world practice (for example, Italian RWE) are expected to further refine management.¹³

Limitations include heterogeneity in endpoint definitions and case-mix definitions across RWE cohorts, which can hinder direct comparability. The absence of individual patient data restricted our ability to perform adjusted analyses. Moreover, temporal improvements in supportive care may bias RWE in a favorable direction relative to older randomized CT. Additionally, the analysis is susceptible to publication and selection biases inherent to study availability and reporting.

Table 2. Summary of the meta-analytic statistical data according to the examined criteria.

Criteria	Entire cohort, % (95% CI)	Statistical data*	RCT, % (95% CI)	RWE, % (95% CI)	P
cCR3	56 (50-61)	Q=82.46 P<0.001 I ² =85%	56 (40-71)	56 (50-62)	0.23
1-year OS	54 (51-57)	Q=51.19 P<0.001 I ² =71%	47(35-60)	55 (52-58)	0.13
Allo-HSCT	38 (33-43)	Q=126.57 P<0.001 I ² =88%	41 (24-59)	38 (32-43)	0.193
30-day mortality	6 (5-8)	Q=12.44 P=0.13 I ² =36%	6 (3-9)	6 (5-8)	0.587
60-day mortality	10 (7-13)	Q=50.76 P<0.001 I ² =80%	13 (9-18)	9 (6-13)	0.03

*Heterogeneity quantified. RCT: randomized controlled trials; RWE: real-world evidence; cCR3: composite complete response; OS: overall survival; Allo-HSCT: allogeneic hematopoietic stem-cell transplantation.

Prospective registries with standardized phenotyping aligned to WHO/ICC criteria, harmonized response definitions, and comprehensive molecular risk profiling (including *TP53* status, complex karyotype, and *NPM1/FLT3* mutations), together with systematic documentation of transplant intent, are essential to enable more granular benchmarking and direct comparisons with alternative induction regimens such as venetoclax plus hypomethylating agents in elderly or unfit patients. Incorporating quality-of-life assessments and health-economic evaluations alongside clinical effectiveness would provide a more holistic basis for informed therapeutic decision-making.

In summary, this synthesis of 16 studies involving over 3,200 patients confirms that CPX-351 achieves consistent remission rates (~56%), low early mortality (~6% at 30 days), and meaningful bridge-to-transplant rates (~38-41%) across both RCT and real-world contexts. The 1-year OS in pooled RWE (~55%) is not inferior - and may modestly exceed - that of RCT populations, likely reflecting differences in patient selection and care delivery. These findings reinforce the external validity of CPX-351 as the induction therapy of choice for secondary/high-risk AML, including AML-MR and t-AML under current classification systems.

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Disclosures

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Contributions

SP, MM conceived this article. DG performed statistical analysis, elaborated graphics. MM wrote the first draft of the article. All the authors read, wrote, critically revised and approved the final manuscript.

Data-sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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