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V-RULES: Real-World Effectiveness and Safety of CPX-351 in Patients With Secondary Acute Myeloid Leukemia (AML)

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Background

- Secondary AML accounts for approximately 25% of all AML cases and is associated with poor outcomes[1,2]
- CPX-351, a dual-drug liposomal encapsulation of daunorubicin and cytarabine in a synergistic 1:5 molar ratio, has demonstrated improved survival in patients with secondary AML when used as frontline therapy[3] and is approved for newly diagnosed, therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC) in adult and pediatric (aged ≥1 year) patients in the United States (US) and adults in Europe[4-6]
  - The approval of CPX-351 was based on the pivotal phase 3 trial (ClinicalTrials.gov identifier: NCT01696084), in which CPX-351 demonstrated significantly improved overall survival (OS) and remission rates vs conventional 7+3 chemotherapy, and a comparable safety profile in older adults aged 60-75 years with newly diagnosed, high-risk or secondary AML[3,7]
- Real-world studies complement findings from clinical trials by providing evidence of treatment effectiveness and safety in diverse real-world populations and healthcare settings to support clinical decision-making[8]

Objective

- To assess real-world effectiveness and safety of CPX-351 in routine clinical practice for US patients with newly diagnosed secondary AML, specifically t-AML or AML-MRC

Methods

- Vyxeos Real-world US Long-term Effectiveness and Safety (V-RULES) was a retrospective, multicenter, single-arm, observational study conducted at 10 US centers
  - Pseudonymized data were collected from medical records of eligible patients with newly diagnosed t-AML or AML-MRC (according to the World Health Organization [WHO] criteria 2016 or 2022) who received ≥1 infusion of CPX-351 monotherapy since its Food and Drug Administration approval in August 2017 in routine US clinical practice
- Primary outcomes were complete response (CR), CR with partial hematologic recovery (CRh), CR with incomplete platelet or neutrophil recovery (CRi), and OS
- Secondary outcomes included rate of hematopoietic cell transplantation (HCT), OS landmarked from HCT date (to better understand post-transplant prognosis), and safety of CPX-351, and are also reported here
  - Adverse events (AEs) of special interest were defined as duration of myelosuppression, severe infections, and bleeding events; local tissue necrosis; cardiac events; and gastrointestinal toxicity
- The study was designed to be descriptive, without hypothesis testing

Results

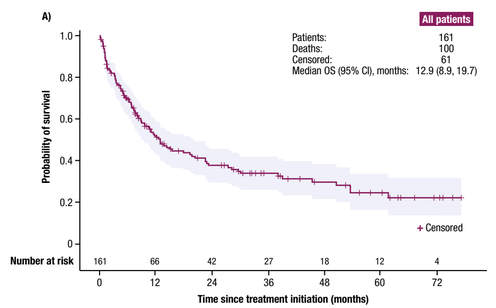
Table 1. Baseline Patient and Disease Characteristics

	Overall (N=161)
Age at AML diagnosis	
Median, years (range)	60 (21, 78)
<60 years, n (%)	78 (48)
≥60 years, n (%)	83 (52)
Male,[a] n (%)	94 (58)
Race,[b] n (%)	
American Indian or Alaska Native	1 (0.6)
Asian	5 (3)
Black or African American	21 (13)
White	116 (73)
Other	15 (9)
Ethnicity, n (%)	
Hispanic or Latino	18 (11)
Not Hispanic or Latino	136 (84)
Unknown	7 (4)
ECOG PS,[c] n (%)	
0	37 (28)
1	78 (60)
2	13 (10)
3	3 (2)
Missing, n	30
AML subtype, n (%)	
t-AML	47 (29)
AML-MRC	114 (71)
Prior MDS[d]	32 (28)
Prior CMML[d]	4 (4)
MDS-related cytogenetic abnormalities[d]	69 (60)
Multilineage dysplasia alone[d]	9 (8)
Grimwade cytogenetic classification,[e] n (%)	
Favorable	9 (6)
Intermediate	57 (37)
Adverse	88 (57)
Molecular abnormalities, n (%)	
TP53 mutation[f]	33 (25)
Myelodysplasia-related gene mutations[g]	57 (63)
Charlson comorbidity index, mean (SD)	1.8 (2.1)

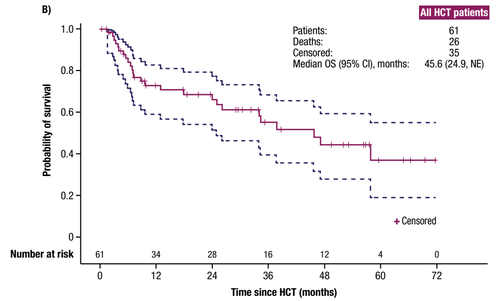
Percentages may not add to 100% due to rounding.
[a]Biological sex; [b]Multi-response question; 5 patients had missing data for race. Percentages were calculated out of total number of patients with non-missing data; [c]Percentages were calculated out of total number of patients with non-missing data; [d]Percentages were calculated out of 114 patients with AML-MRC; [e]7 patients had missing data for Grimwade cytogenetic classification. Percentages were calculated out of total number of patients with non-missing data; [f]27 patients had missing data for mutated *TP53*. Percentages were calculated out of total number of patients with non-missing data; [g]Myelodysplasia-related mutations were defined as mutations in *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2*. Percentages were calculated out of 91 patients with data collected for myelodysplasia-related mutations.
AML, acute myeloid leukemia; AML-MRC, acute myeloid leukemia with myelodysplasia-related changes; CMML, chronic myelomonocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; MDS, myelodysplastic syndrome; SD, standard deviation; t-AML, therapy-related acute myeloid leukemia; *TP53*, tumor protein p53.

- All 161 patients (t-AML, 47/161 [29%]; AML-MRC, 114/161 [71%]) received ≥1 induction of CPX-351, with the vast majority receiving 1 induction (1 cycle, 142/161 [88%]; 2 cycles, 19/161 [12%]), and 50 patients received consolidation (1 cycle, 40/161 [25%]; 2 cycles, 10/161 [6%])
- Median follow-up time was 9.7 months (interquartile range: 4.1, 27.8)

Figure 1. Kaplan-Meier Plots for OS (A) From CPX-351 Treatment Initiation and (B) Landmarked From HCT Date



	All patients	
Time point	n at risk	Probability of survival (95% CI)
2 years	42	0.37 (0.29, 0.45)
3 years	27	0.34 (0.26, 0.42)
4 years	18	0.29 (0.21, 0.38)

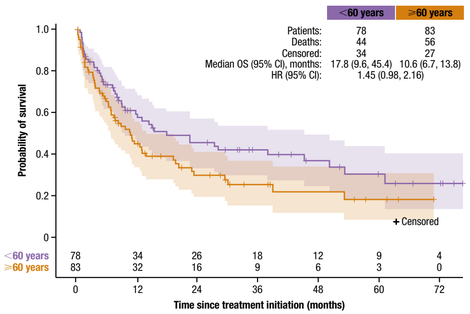


	All HCT patients	
Time point	n at risk	Probability of survival (95% CI)
2 years	28	0.68 (0.54, 0.79)
3 years	16	0.55 (0.39, 0.68)
4 years	12	0.44 (0.28, 0.59)

(A) OS curve is shown with its 95% CIs (shaded area). (B) OS curve is shown with its 95% Hall-Wellner Band (dotted lines).
CI, confidence interval; HCT, hematopoietic cell transplantation; n, number; NE, not estimated; OS, overall survival.

- Median OS was 12.9 months (95% confidence interval [CI]: 8.9, 19.7), and Kaplan-Meier (KM)–estimated 4-year OS was 29% (95% CI: 21, 38)
- Estimated mortality since the date of CPX-351 treatment initiation was 8% by day 30 and 16% by day 60
- Patients who underwent HCT after CPX-351 treatment (38%) had prolonged survival (median OS: 45.6 months [95% CI: 24.9, not estimated]; KM-estimated 4-year OS: 44% [95% CI: 28, 59]) compared with the overall population

Figure 2. Kaplan-Meier Plot for OS From CPX-351 Treatment Initiation for Patients Aged <60 Years vs ≥60 Years

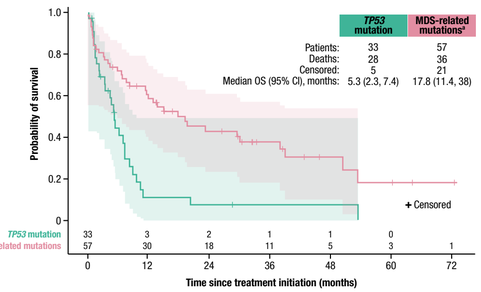


	<60 years		≥60 years	
Time point	n at risk	Probability of survival (95% CI)	n at risk	Probability of survival (95% CI)
2 years	26	0.45 (0.33, 0.57)	16	0.30 (0.19, 0.41)
3 years	18	0.42 (0.30, 0.54)	9	0.25 (0.15, 0.37)
4 years	12	0.37 (0.24, 0.49)	6	0.22 (0.12, 0.34)

OS curves are shown with 95% CIs (light-shaded area).
CI, confidence interval; HR, hazard ratio; n, number; OS, overall survival.

- Median OS was 17.8 months (95% CI: 9.6, 45.4) in younger patients (aged <60 years) vs 10.6 months (95% CI: 6.7, 13.8) in older patients (aged ≥60 years; hazard ratio: 1.45; 95% CI: 0.98, 2.16)

Figure 3. Kaplan-Meier Plot for OS From CPX-351 Treatment Initiation According to Mutation Status



	TP53 mutation		MDS-related mutations[a]	
Time point	n at risk	Probability of survival (95% CI)	n at risk	Probability of survival (95% CI)
2 years	2	0.07 (0.01, 0.21)	18	0.43 (0.29, 0.56)
3 years	1	0.07 (0.01, 0.21)	11	0.38 (0.24, 0.51)
4 years	1	0.07 (0.01, 0.21)	5	0.30 (0.17, 0.45)

OS curves are shown with 95% CIs (light-shaded area).
[a]Myelodysplasia-related mutations were defined as mutations in *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2*.
CI, confidence interval; MDS, myelodysplastic syndrome; n, number; OS, overall survival; *TP53*, tumor protein p53.

- Survival outcomes varied by genetic mutations, with shorter median OS in patients with *TP53* mutations (5.3 months [95% CI: 2.3, 7.4]) and numerically longer median OS in patients with myelodysplasia-related gene mutations (17.8 months [95% CI: 11.4, 38.0]), compared with the overall population

Table 2. Response Rates

	Overall (N=161)
CR (including MRD-negativity) or CRh/CRi,[a] n (%)	
Yes [95% CI]	94 (63) [55, 71]
No	55 (37)
Missing, n	12
Best response achieved,[a] n (%)	
CR/CRh/CRi without MRD [95% CI]	34 (23) [16, 30]
CR [95% CI]	43 (29) [22, 37]
CRh [95% CI]	8 (5) [2, 10]
CRi [95% CI]	9 (6) [3, 11]
MLFS	6 (4)
PR	5 (3)
Treatment failure	44 (30)
Missing, n	12

CIs were based on the Clopper-Pearson exact method.
[a]Best response achieved during all CPX-351 cycles of each patient.
CI, confidence interval; CR, complete response; CRh, complete response with partial hematologic recovery; CRi, complete response with incomplete platelet or neutrophil recovery; MLFS, morphologic leukemia-free state; MRD, minimal residual disease; PR, partial response.

- CR (including minimal residual disease [MRD] negativity)/CRh/CRi at any time was 63% in 149 evaluable patients (t-AML, 85%; AML-MRC, 53%)
  - CR (including MRD negativity)/CRh/CRi at any time was 65% (95% CI: 54, 76) for patients aged <60 years and 61% (95% CI: 49, 72) for patients aged ≥60 years
- MRD test (predominantly by flow cytometry) results were available for 90 (56%) patients at any time; among them, 36 (40%) had at least one negative MRD test result
- Among 86 patients who achieved CR/CRh/CRi or CR/CRh/CRi including MRD negativity after induction 1, 57 (66%) had MRD testing and 28 (49%) patients were MRD-negative

Table 3. Grade 3-5 TEAEs of Special Interest During CPX-351 Treatment

	Highest Severity (All Patients; N=161)[b]			
TEAE,[a] n (%)	Grades 3-5	Grade 3	Grade 4	Grade 5
Infection	73 (45)	55 (34)	13 (8)	5 (3)
Febrile neutropenia	65 (40)	63 (39)	2 (1)	0
Bleeding	33 (20)	30 (19)	1 (0.6)	2 (1)
Gastrointestinal toxicity	15 (9)[b]	14 (9)	0	0
Cardiac events	12 (7)	11 (7)	0	1 (0.6)

[a]Defined as AE during CPX-351 treatment between first infusion and last infusion plus 30 days; [b]Percentages calculated over the total number of patients with non-missing severity.
TEAE, treatment-emergent adverse event.

- Overall, 148 (92%) patients had at least one grade ≥3 AE (all-cause)
- In total, 42 (26%) patients reported at least one serious treatment-related AE

Table 4. Hematological Recovery Times in Patients Achieving CR/CRh/CRi

	Induction 1	Consolidation 1
Time to neutrophil recovery (≥500/μL)	n=76	n=27
Median (IQR), days	35 (29, 40)	27 (24, 30)
Prolonged neutrophil myelosuppression beyond day 42, n (%)	16 (20)	2 (7)
Time to platelet recovery (≥50,000/μL)	n=72	n=25
Median (IQR), days	36 (31, 46)	27.5 (22, 37)
Prolonged platelet myelosuppression beyond day 42, n (%)	24 (30)	6 (21)

CR, complete response; CRh, complete response with partial hematologic recovery; CRi, complete response with incomplete platelet or neutrophil recovery; IQR, interquartile range.

- Among patients who achieved CR/CRh/CRi after induction 1, the median time to neutrophil (≥500/μL) and platelet (≥50,000/μL) recovery was 35 days and 36 days, respectively

Conclusions

- V-RULES supports the effectiveness and safety of CPX-351 for the treatment of patients with newly diagnosed t-AML or AML-MRC in the US real-world setting
- Consistent with the pivotal trial and other published real-world data,[3,9] these results suggest that CPX-351 may offer potential benefits in terms of response rates and survival outcomes in this high-risk patient population (63% of patients had myelodysplasia-related gene mutations; 57% of patients were adverse risk; 25% of patients had mutated *TP53*)
- In addition, this study indicates that CPX-351 is effective and safe for younger patients (aged <60 years) who were not included in the pivotal trial[3] but for whom CPX-351 is an important treatment option[10,11]
- Patients with myelodysplasia-related gene mutations also benefited from CPX-351, consistent with recently presented data[12] and the updated 2022 WHO and International Consensus Classification guidelines[13,14]
- Safety in the V-RULES study was consistent with the known safety profile of CPX-351[3,9]
- Study limitations align with those typically associated with retrospective research
- These results reinforce CPX-351 as the standard of care for patients with newly diagnosed t-AML or AML-MRC who are eligible for intensive chemotherapy

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