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V-RULES: Impact of Treatment Setting on CPX-351 Safety and Effectiveness in Secondary Acute Myeloid Leukemia

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Background

- Patients with acute myeloid leukemia (AML) have traditionally received intensive chemotherapy (IC) in the inpatient setting due to the need for continuous infusion and close monitoring of potential IC-related toxicities, resulting in substantial healthcare resource utilization (HCRU)[1-3]
  - Conventional 7+3 chemotherapy is administered as 7 days continuous infusion of cytarabine + 3 days of once-daily injections of an anthracycline,[4] whereas CPX-351 is administered as 1 90-minute infusion (on days 1, 3, and 5 for first induction and days 1 and 3 for subsequent cycles), and, therefore, may be more amenable to administration in an outpatient setting[1,5,6]
- HCRU analyses of the CPX-351 vs 7+3 pivotal phase 3 trial in older adults with newly diagnosed high-risk or secondary AML showed that CPX-351, in addition to significantly improving overall survival (OS) and remission rate vs 7+3, was associated with shorter hospital stays and comparable supportive care use[1,6]
- Similarly, the real-world CREST-UK study reported that outpatient treatment with CPX-351 was feasible for all treatment stages, with the outpatient setting associated with a reduced need for hospital treatment in the UK healthcare system[7]
- The Vyxeos Real-world US Long-term Effectiveness and Safety (V-RULES) study highlighted the real-world effectiveness and safety of CPX-351 in US patients with newly diagnosed secondary AML,[8] and provides an opportunity to explore real-world CPX-351 HCRU within the US healthcare system

Objective

- To report hospitalization incidence and duration, and effectiveness and safety of CPX-351 by treatment setting (inpatient vs outpatient) in the V-RULES study

Methods

- V-RULES was a retrospective, multicenter, single-arm, observational study
  - Pseudonymized data were collected from medical records of eligible patients with newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC; according to the World Health Organization criteria 2016 or 2022) who received ⩾1 infusion of CPX-351 monotherapy in routine practice between October 26, 2017, and May 29, 2024, at 10 US centers
- Patient selection for delivery setting and dosing schedules were based on local decisions and policies
- Effectiveness and safety were assessed in patients who received ⩾2 CPX-351 cycles to align and compare with the CREST-UK study,[7] and patients who only received one induction and no subsequent cycles were excluded from the analysis
- Descriptive statistics were used to report HCRU and safety by delivery setting (inpatient vs outpatient)
- Effectiveness was reported by delivery setting (inpatient vs outpatient)
  - OS was estimated using the Kaplan-Meier method
  - Response was assessed according to the European LeukemiaNet 2022 response assessment criteria[9]
- The study was designed to be descriptive, without hypothesis testing

Results

Table 1. Baseline Patient and Disease Characteristics in the Overall V-RULES Population and by Delivery Type After First Induction

	Overall (N=161)	Inpatients[a] (n=21)	Outpatients[b] (n=43)
Age at AML diagnosis			
Median, years (range)	60 (21, 78)	65 (47, 71)	61 (40, 75)
<60 years, n (%)	78 (48)	7 (33)	18 (42)
⩾60 years, n (%)	83 (52)	14 (67)	25 (58)
Male,[c] n (%)	94 (58)	11 (52)	23 (53)
Race,[d] n (%)			
American Indian or Alaska Native	1 (0.6)	1 (5)	0
Asian	5 (3)	0	2 (5)
Black or African American	21 (13)	2 (10)	4 (10)
White	116 (73)	17 (81)	31 (76)
Other	15 (9)	1 (5)	6 (15)
Ethnicity, n (%)			
Hispanic or Latino	18 (11)	1 (5)	6 (14)
Not Hispanic or Latino	136 (84)	19 (90)	36 (84)
Unknown	7 (4)	1 (5)	1 (2)
ECOG PS,[e] n (%)			
0	37 (28)	3 (18)	11 (31)
1	78 (60)	14 (82)	20 (56)
2	13 (10)	0	4 (11)
3	3 (2)	0	1 (3)
Missing, n	30	4	7
AML subtype, n (%)			
t-AML	47 (29)	5 (24)	18 (42)
AML-MRC	114 (71)	16 (76)	25 (58)
Prior MDS[f]	32 (28)	3 (19)	5 (20)
Prior CMML[f]	4 (4)	0	2 (8)
MDS-related cytogenetic abnormalities[f]	69 (60)	11 (69)	16 (64)
Multilineage dysplasia alone[f]	9 (8)	2 (12)	2 (8)
Grimwade cytogenetic classification,[g] n (%)			
Favorable	9 (6)	0	3 (7)
Intermediate	57 (37)	7 (35)	19 (44)
Adverse	88 (57)	13 (65)	21 (49)
Molecular abnormalities, n (%)			
TP53 mutation[h]	33 (25)	7 (44)	6 (17)
MDS-related gene mutations[i]	57 (63)	6	16
Charlson Comorbidity Index, mean (range)	1 (0, 12)	2 (0, 12)	2 (0, 8)

Percentages may not add to 100% due to rounding.

[a]Patients who received all cycles of CPX-351 after first induction as inpatients; [b]Patients who received ⩾1 cycle of CPX-351 after first induction as outpatients; [c]Biological sex; [d]Multi-response question; 2 outpatients had missing data for race. Percentages were calculated out of total number of patients with non-missing data; [e]Percentages were calculated out of total number of patients with non-missing data; [f]Percentages were calculated out of 16 inpatients and 25 outpatients with AML-MRC, respectively; [g]7 patients had missing data for Grimwade cytogenetic classification. Percentages were calculated out of total number of patients with non-missing data; [h]27 patients had missing data for mutated *TP53*. Percentages were calculated out of total number of patients with non-missing data; [i]MDS-related mutations were defined as mutations in *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *ZRSR2*. For the overall population, percentage was calculated out of 91 patients with data collected for MDS-related mutations. Percentages are not reported by delivery type as the total number of patients with data collected for MDS-related mutations by delivery type were missing.

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; t-AML, therapy-related acute myeloid leukemia; *TP53*, tumor protein p53; V-RULES, Vyxeos Real-world US Long-term Effectiveness and Safety.

- In V-RULES, 161 patients (t-AML: 47/161 [29%]; AML-MRC: 114/161 [71%]) received between ⩾1 and ⩽4 cycle(s) of CPX-351
- Overall, 64 patients received ⩾2 cycles of CPX-351: after first induction, 43 patients received ⩾1 subsequent cycle(s) as outpatients, and 21 patients received all subsequent cycles as inpatients
- Comparison of outpatient and inpatient subgroups showed similar age (median: outpatients, 61 years [range: 40, 75]; inpatients, 65 years [range: 47, 71]) and Charlson Comorbidity Index (median: outpatients, 2 [range: 0, 8]; inpatients, 2 [range: 0, 12])
- Median follow-up time was 9.7 months (interquartile range: 4.1, 27.8)

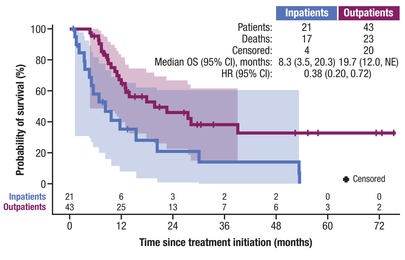
Table 2. Hospitalization Incidence and Duration by Delivery Setting During CPX-351 Induction and Consolidation

	Overall	Inpatients	Outpatients	Outpatients who required hospitalization
Induction 1				
Number of patients, n (%)	161 (100)	134 (83)	27 (17)	20 (74)
Days in ward, median (Q1, Q3)	32 (22, 40)[a]	33 (26, 41)	22 (0, 34)[a]	26 (22, 34)[a]
Induction 2				
Number of patients, n (%)	19 (100)	17 (89)	2 (11)	1 (50)
Days in ward, median (Q1, Q3)	32 (4, 43)	33 (28, 43)	5 (0, 10)	10 (10, 10)
Consolidation 1				
Number of patients, n (%)	50 (100)	9 (18)	41 (82)	10 (24)
Days in ward, median (Q1, Q3)	0 (0, 4)	8 (6, 27)	0 (0, 0)	4 (3, 16)
Consolidation 2				
Number of patients, n (%)	10 (100)	1 (10)	9 (90)	2 (22)
Days in ward, median (Q1, Q3)	0 (0, 4)	45 (45, 45)	0 (0, 0)	8 (4, 11)

[a]Data were missing for 1 patient.
Q1, quartile 1; Q3, quartile 3.

- For all stages of treatment with CPX-351, patients treated in the outpatient setting had shorter hospital stays compared with patients treated in the inpatient setting
- Patients who received outpatient treatment with CPX-351 spent a median of 11, 28, 8, and 45 days fewer on the ward compared with inpatient administration during first induction (n=27), second induction (n=2), first consolidation (n=41), and second consolidation (n=9), respectively
- Regardless of treatment setting, no patients required intensive care unit (ICU) support during first induction, second induction, or first consolidation; during second consolidation, 2 patients initially treated as outpatients required ICU support (median of 4 days in ICU)

Figure 1. Kaplan-Meier–Estimated OS by Delivery Setting After First Induction



Time point	Inpatients: n at risk	Inpatients: Probability of survival (95% CI)	Outpatients: n at risk	Outpatients: Probability of survival (95% CI)
1 year	6	35.3 (14.9, 56.5)	25	64.9 (47.9, 77.5)
2 years	3	21.2 (5.7, 43.1)	13	46.1 (29.1, 61.5)
3 years	2	14.1 (2.5, 35.4)	7	38.4 (22.0, 54.7)
4 years	2	14.1 (2.5, 35.4)	6	32.9 (16.6, 50.3)

OS curves are shown with their 95% CIs (shaded area).
CI, confidence interval; HR, hazard ratio; n, number; NE, not estimated; OS, overall survival.

- For patients who received ⩾2 cycles of CPX-351, median OS was 8.3 months (95% confidence interval [CI]: 3.5, 20.3) for inpatients and 19.7 months (95% CI: 12.0, not estimated) for outpatients, with an estimated 4-year OS of 14% and 33%, respectively

Table 3. Response Rates by Delivery Setting

	Overall (N=161)	Inpatients[a] (n=21)	Outpatients[b] (n=43)
CR (including MRD-negativity) or CRh/CRi[c]			
Yes, n (%) [95% CI]	94 (63) [55, 71]	12 (60) [36, 81]	41 (95) [84, 99]
No, n (%)	55 (37)	8 (40)	2 (5)
Missing, n	12	1	0
Best response achieved[c]			
CR/CRh/CRi without MRD, n (%) [95% CI]	34 (23) [16, 30]	4 (20) [6, 44]	17 (40) [25, 56]
CR, n (%) [95% CI]	43 (29) [22, 37]	3 (15) [3, 38]	21 (49) [33, 64]
CRh, n (%) [95% CI]	8 (5) [2, 10]	2 (10) [1, 32]	3 (7) [2, 19]
CRi, n (%) [95% CI]	9 (6) [3, 11]	3 (15) [3, 38]	0 [NA]
MLFS, n (%)	6 (4)	1 (5)	1 (2)
PR, n (%)	5 (3)	2 (10)	1 (2)
Treatment failure, n (%)	44 (30)	5 (25)	0
Missing, n	12	1	0

95% CIs are percentages.

[a]Patients who received all cycles of CPX-351 after first induction as inpatients; [b]Patients who received ⩾1 cycle of CPX-351 after first induction as outpatients; [c]Best response achieved in any cycle with CPX-351.

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; NA, not applicable; PR, partial response.

- For patients who received ⩾2 cycles of CPX-351, complete response (CR)/CR with partial hematologic recovery/CR with incomplete platelet or neutrophil recovery was observed in a majority of patients, with a notable difference between inpatients and outpatients: 60% (12/20) of inpatients and 95% (41/43) of outpatients achieved this outcome

Table 4. AEs by Delivery Setting

	Overall (N=161)	Inpatients[a] (n=21)	Outpatients[b] (n=43)
Serious TEAEs,[c] n (%)	64 (40)	8 (38)	10 (23)
Grade ⩾3 TEAEs,[c] n (%)	132 (82)	19 (90)	34 (79)
Grade ⩾3 TRAEs, n (%)	120 (75)	18 (86)	33 (77)

[a]Patients who received all cycles of CPX-351 after first induction as inpatients; [b]Patients who received ⩾1 cycle of CPX-351 after first induction as outpatients; [c]Defined as any TEAE reported between first CPX-351 infusion and last CPX-351 infusion plus 30 days.
AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

- For patients who received ⩾2 cycles of CPX-351 compared with patients treated in the inpatient setting, patients treated in the outpatient setting had a lower rate of serious treatment-emergent adverse events (TEAEs), grade ⩾3 TEAEs, and grade ⩾3 treatment-related adverse events

Conclusions

- In the V-RULES study, outpatient delivery of CPX-351 in the US was feasible, especially during consolidation, with a reduction in hospitalization incidence and duration, and did not appear to be associated with mortality or increased adverse events compared with inpatient treatment
- These results are consistent with those observed in the UK healthcare system from the CREST-UK study and highlight important potential resource benefits of outpatient CPX-351 treatment[7]
- Together, the data from the V-RULES and CREST-UK studies reinforce the outpatient results from post hoc analyses of the CPX-351 phase 3 trial[1,6]
- The V-RULES study showed favorable survival and response rates in the outpatient setting; however, these results should be interpreted within the context of the study's limitations. The observed differences in patient outcomes by delivery setting may be attributable to patient characteristics and treatment setting decisions based on clinical judgment. Further exploratory analyses are needed to identify the underlying patient characteristics that may impact survival and response outcomes
- The V-RULES findings provide insights into real-world use of CPX-351 in US patients with t-AML or AML-MRC, highlighting an opportunity for outpatient treatment for some patients

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