5215 Effectiveness and Safety of CPX-351 in Younger Patients <60 Years With Newly Diagnosed Secondary Acute Myeloid Leukemia: Pooled Analysis of US (V-RULES) and UK (CREST-UK) Real-World Studies

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Background

- CPX-351 is a dual-drug liposomal encapsulation of daunorubicin and cytarabine in a synergistic 1:5 molar ratio that is approved for newly diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC) in patients aged ⩾1 year in the US and adult patients in the UK/EU[1-4]
  - These approvals were based on the pivotal phase 3 trial (ClinicalTrials.gov identifier: NCT01696084) of CPX-351 vs 7+3 chemotherapy in adults aged 60-75 years with high-risk/secondary AML showing significantly improved efficacy (median overall survival [OS]: 9.56 vs 5.95 months, one-sided *P*=0.003; complete remission [CR]/CR with incomplete platelet or neutrophil recovery [CRi]: 47.7% vs 33.3%, two-sided *P*=0.016) and comparable safety[1]
- Real-world studies complement the knowledge gained from clinical trials by providing evidence of treatment effectiveness and safety in broader patient populations, therefore, addressing data gaps and supporting clinical decision-making[5]
- Two real-world studies, V-RULES (Vyxeos Real-world US Long-term Effectiveness and Safety)[6] and CREST-UK (CPX-351 Real-world Effectiveness and SafeTy Study; NCT05169307)[7] were conducted in the US and UK, respectively, and highlighted the real-world effectiveness and safety of CPX-351 in adults with newly diagnosed t-AML or AML-MRC

Objective

- To assess the real-world effectiveness and safety of CPX-351 in adult patients aged <60 years with newly diagnosed t-AML or AML-MRC from a pooled analysis of the V-RULES and CREST-UK studies

Methods

- V-RULES and CREST-UK are retrospective, single-arm studies that collected pseudonymized data from the medical records of patients with newly diagnosed t-AML or AML-MRC who received ⩾1 infusion of CPX-351 in routine practice after FDA/EU approval
  - V-RULES was conducted at 10 US centers (October 2017-May 2024) and CREST-UK at 15 UK centers (November 2018-March 2022)
- The two studies were developed and designed at different times, and thus, some of the data collection methods differed
- Response definitions differed between the two studies (defined as CR/CR with partial hematologic recovery [CRh]/CRi in V-RULES, and CR/CRi in CREST-UK) and were compared side by side in this pooled analysis
- Pooled outcomes were Kaplan-Meier (KM)-estimated OS and safety

Results

- Overall, 134 patients aged <60 years (V-RULES, N=78; CREST-UK, N=56) received ⩾1 induction cycle of CPX-351 (1 cycle, n=114; 2 cycles, n=19; 3 cycles, n=1)
- The median follow-up time was 12.1 months (quartile 1, quartile 3: 5.5, 27.5)

Table 1. Baseline Patient and Disease Characteristics

	Overall (N=134)
Age at AML diagnosis	
Median, years (min, max)	52 (18, 59)
18-24 years, n (%)	7 (5)
25-59 years, n (%)	127 (95)
Male,[a] n (%)	74 (55)
ECOG PS,[b] n (%)	
0	45 (41)
1	55 (50)
2	10 (9)
3	1 (0.9)
Missing, n	23
AML subtype, n (%)	
t-AML	47 (35)
AML-MRC	87 (65)
Grimwade cytogenetic classification,[c] n (%)	
Favorable	6 (5)
Intermediate	54 (42)
Adverse	70 (54)
Molecular abnormalities, n (%)	
TP53 mutations[d]	25 (24)
MDS-related gene mutations[e]	35 (37)
Key cytogenic abnormalities, n (%)	
Normal karyotype[f]	31 (24)
Monosomal karyotype[f]	15 (11)
Complex karyotype (3 or more abnormalities)[f]	34 (26)

Percentages may not add up to 100 due to rounding.

[a]Biological sex; [b]Percentages were calculated out of total number of patients with non-missing data; [c]Two patients had unknown data and 2 patients had missing data for Grimwade cytogenic classification. Percentages were calculated out of total number of patients with available data; [d]29 patients had missing data for *TP53* mutations. Percentages were calculated out of total number of patients with non-missing data; [e]MDS-related gene mutations were defined as mutations in *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2,* and excluded mutations in *TP53*. Six patients had both MDS-related mutations and *TP53* mutations and were excluded; [f]Key cytogenetic abnormalities are shown. This was a multi-response question and reported only for tested patients. Three patients were not tested/had unknown results. Percentages were calculated out of total number of patients tested for cytogenic abnormalities.

AML, acute myeloid leukemia; AML-MRC, acute myeloid leukemia with myelodysplasia-related changes; ECOG PS, Eastern Cooperative Oncology Group performance status; MDS, myelodysplasia; t-AML, therapy-related acute myeloid leukemia; *TP53*, tumor protein p53.

Table 2. Response Rates

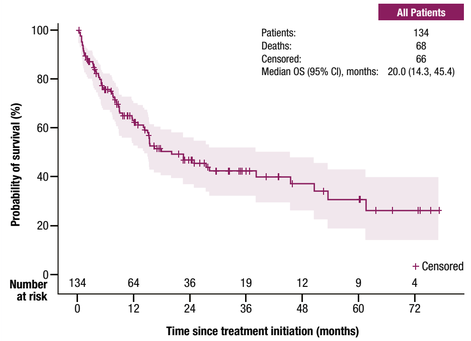
	V-RULES[a] (N=78)	CREST-UK (N=56)
CR/CRh/CRi,[b] n (%)		
Yes [95% CI]	49 (65) [54, 76]	–
No	26 (35)	–
CR/CRi,[c] n (%)		
Yes [95% CI]	–	37 (66) [52, 78]
No	–	19 (34)
Best response achieved,[d] n (%)		
CR/CRh/CRi with MRD negativity [95% CI][b]	13 (17) [10, 28]	–
CR with MRD negativity [95% CI][e]	–	9 (16) [8, 28]
CR [95% CI]	25 (33) [23, 45]	20 (36) [23, 50]
CRh [95% CI]	6 (8) [3, 17]	–
CRi [95% CI]	5 (7) [2, 15]	8 [6, 26]
MLFS	1 (1)	2 (4)
PR	2 (3)	2 (4)
Treatment failure	23 (31)	15 (27)

[a]Three patients with missing data. Percentages were calculated out of total number of patients with non-missing data; [b]In V-RULES, response was defined as CR/CRh/CRi; [c]In CREST-UK, response was defined as CR/CRi; [d]Best response achieved during all CPX-351 cycles of each patient; [e]In CREST-UK, best response with MRD negativity was collected for patients who achieved CR only.

CI, confidence interval; CR, complete response; CREST-UK, CPX-351 Real-world Effectiveness and SafeTy Study; CRh, complete response with partial hematologic recovery; CRi, complete response with incomplete platelet or neutrophil recovery; MLFS, morphologic leukemia-free state; MRD, measurable residual disease; PR, partial response; V-RULES, Vyxeos Real-world US Long-term Effectiveness and Safety.

- Among evaluable patients, CR/CRh/CRi was achieved by 49/75 (65%) in V-RULES and CR/CRi was achieved by 37/56 (66%) in CREST-UK
- Among responders, measurable residual disease (MRD) status at best response was assessed in 50 patients (most commonly by flow cytometry) and 22/50 (44%) patients were MRD-negative

Figure 1. Kaplan-Meier Plot for OS From CPX-351 Treatment Initiation

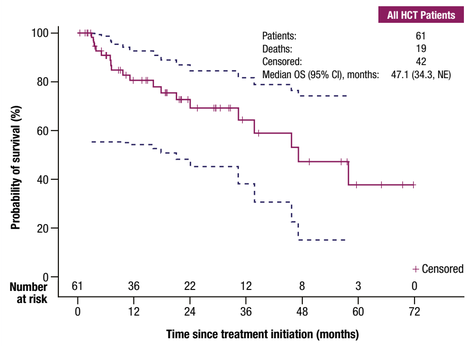


	All Patients	
Time Point	n at Risk	Probability of Survival, % (95% CI)
3 years	19	42 (32, 52)
4 years	12	37 (26, 48)

OS is shown with its 95% CI (shaded area).
CI, confidence interval; OS, overall survival.

- Median OS was 20.0 months (95% confidence interval [CI]: 14.3, 45.4), with a KM-estimated 4-year OS of 37% (95% CI: 26%, 48%)
- Early mortality was 6% by day 30 and 11% by day 60

Figure 2. Kaplan-Meier Plot for OS Landmarked From HCT Date

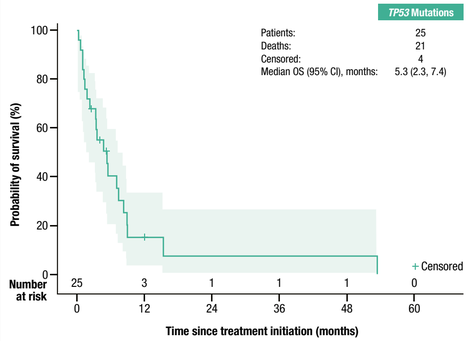


	All HCT Patients	
Time Point	n at Risk	Probability of Survival, % (95% CI)
3 years	12	64 (46, 78)
4 years	8	47 (26, 66)

OS is shown with its 95% Hall-Wellner Band (dotted lines).
CI, confidence interval; HCT, hematopoietic cell transplantation; NE, not estimable; OS, overall survival.

- In total, 61/134 (46%) patients underwent hematopoietic cell transplantation (HCT) after CPX-351 treatment
- Median OS post-HCT was 47.1 months (95% CI: 34.3, not estimated [NE]), with an estimated 4-year OS of 47% (95% CI: 26%, 66%)

Figure 3. Kaplan-Meier Plot for OS From CPX-351 Treatment Initiation in Patients With *TP53* Mutations

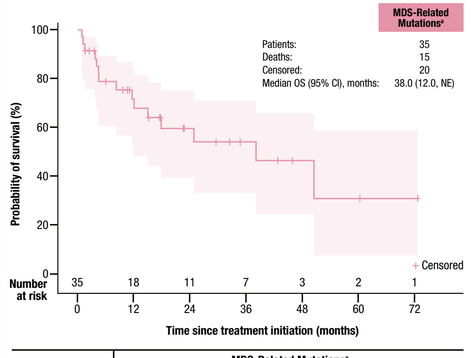


	TP53 Mutations	
Time Point	n at Risk	Probability of Survival, % (95% CI)
3 years	1	8 (1, 27)
4 years	1	8 (1, 27)

OS is shown with its 95% CI (shaded area).
CI, confidence interval; OS, overall survival; *TP53*, tumor protein p53.

- In patients with *TP53* mutations, median OS was 5.3 months (95% CI: 2.3, 7.4)

Figure 4. Kaplan-Meier Plot for OS From CPX-351 Treatment Initiation in Patients With MDS-Related Mutations[a]



	MDS-Related Mutations[a]	
Time Point	n at Risk	Probability of Survival, % (95% CI)
3 years	7	54 (33, 71)
4 years	3	46 (24, 66)

OS is shown with its 95% CI (shaded area).
[a]MDS-related gene mutations were defined as mutations in *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2,* and excluded mutations in *TP53*. Six patients had both MDS-related mutations and *TP53* mutations and were excluded.
CI, confidence interval; MDS, myelodysplasia; NE, not estimable; OS, overall survival; *TP53*, tumor protein p53.

- In patients with myelodysplasia (MDS)-related mutations, median OS was 38.0 months (95% CI: 12.0, NE), with a KM-estimated 4-year OS of 46% (95% CI: 24%, 66%)

Table 3. Safety During CPX-351 Treatment

	Highest Severity (All Patients; N=134)			
	Grades 3-5	Grade 3	Grade 4	Grade 5
TEAE, n (%)				
Febrile neutropenia	61 (46)	60 (45)	0	1 (0.7)
Infection	52 (39)	40 (30)	10 (7)	2 (1)
Bleeding	20 (15)	18 (13)	2 (1)	0
Treatment-related TEAE, n (%)				
Pericarditis, myocarditis, endocarditis, cardiomyopathy, arrhythmias, or other rhythm abnormalities	6 (4)	5 (4)	1 (0.7)	0

TEAE, treatment-emergent adverse event.

- Overall, 100/134 (75%) patients experienced grade ⩾3 treatment-emergent adverse events (TEAEs)
  - Febrile neutropenia and infection were the most common grade ⩾3 TEAEs
- Out of 134 patients, 47 (35%) experienced ⩾1 serious TEAE

Table 4. Hematological Recovery Times in Responders

	Induction 1	Consolidation 1
Time to neutrophil recovery (⩾500/μL)	n=68	n=24
Median (Q1, Q3), days	35 (30, 41)	28 (25, 32)
Prolonged neutrophil myelosuppression beyond day 42, n (%)	15 (22)	3 (12)
Time to platelet recovery (⩾50,000/μL)	n=64	n=22
Median (Q1, Q3), days	37 (32, 44)	27 (22, 36)
Prolonged platelet myelosuppression beyond day 42, n (%)	20 (31)	4 (18)

Q1, quartile 1; Q3, quartile 3.

- In responders, median time to neutrophil (⩾500/μL) and platelet (⩾50,000/μL) recovery after Induction 1 was 35 days and 37 days, respectively

Conclusions

- This pooled analysis of the V-RULES and CREST-UK studies provides valuable real-world data on the effectiveness and safety of CPX-351 in adult patients aged <60 years with t-AML or AML-MRC, which is noteworthy as younger adults were not eligible for inclusion in the CPX-351 phase 3 trial[1]
- We observed more favorable response and survival and a numerically higher HCT rate in adults aged <60 years compared with the population of adults aged 60-75 years who were included in the CPX-351 phase 3 trial[1]
- Survival benefit with CPX-351 was also observed in patients with MDS-related mutations, supporting previous studies[8-10]
- While survival in patients with *TP53* mutations was poor, this is consistent with previous findings and highlights the continued need for alternative treatment options for this patient population with limited benefit from existing treatments[8,11-12]
- Limitations of this study include its retrospective nature with clinician selected treatment in major medical centers and differing definitions for response between the 2 studies
- This retrospective real-world pooled analysis of patients treated at 25 US and UK medical centers demonstrates favorable effectiveness and acceptable tolerability of CPX-351 in younger adults with newly diagnosed t-AML or AML-MRC eligible for intensive chemotherapy

References: 1. Lancet JE, et al. *J Clin Oncol.* 2018;36(26):2684-2692. **2.** VYXEOS® (daunorubicin and cytarabine) liposome for injection, for intravenous use [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; 2022. **3.** Vyxeos liposomal (44 mg/100 mg powder for concentrate for solution for infusion) summary of product characteristics. Electronic Medicines Compendium: Jazz Pharmaceuticals UK, Ltd.; 2025. **4.** Vyxeos liposomal (44 mg/100 mg powder for concentrate for solution for infusion) summary of product characteristics. European Medicines Agency: Jazz Pharmaceuticals Ireland, Ltd.; 2024. **5.** Dang A. *Pharmaceut Med.* 2023;37(1):25-36. **6.** LeBlanc TW, et al. *J Clin Oncol.* 2025;43(16_suppl):6520. **7.** Mehta P, et al. *Br J Haematol.* 2024;205(4):1326-1336. **8.** Shimony SO, et al. *Blood.* 2024;144(Supplement 1):60-61. **9.** Othman J, et al. *Blood Adv.* 2023;7(16):4539-4549. **10.** Mehta P, et al. *Blood.* 2024;144(Supplement 1):55. **11.** Lindsley RC, et al. *Blood.* 2019;134(Supplement 1):15. **12.** Daver NG, et al. *J Hematol Oncol.* 2023;16(1):19.

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TW LeBlanc is a Scholar in Clinical Research of Blood Cancer United.