AML-272

A Phase 3 Study of CPX-351 Versus Conventional 7+3 Cytarabine and Daunorubicin: Subanalysis of Patients With Secondary Acute Myeloid Leukemia (sAML) With Refractory Anemia With Excess of Blasts in Transformation (RAEB-t)

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Background

- Patients with AML or myelodysplastic syndrome (MDS) who have bone marrow blasts of 20% to 30% are considered by the French-American-British classification as having RAEB-t[1]
- The optimal treatment paradigm for patients with RAEB-t is unclear, as they may be treated as having MDS or AML, and thus receive hypomethylating agents (HMAs) or intensive chemotherapy[1-3]
- CPX-351 (Vyxeos®; daunorubicin and cytarabine liposome for injection) has been approved by the US FDA and the EMA for the treatment of adults with newly diagnosed, therapy-related AML or AML with myelodysplasia-related changes[4,5]
- In a phase 3 trial of older adults (aged 60-75 years) with newly diagnosed sAML that compared CPX-351 with conventional 7+3, median overall survival (OS) was prolonged with CPX-351 (9.56 vs 5.95 months; hazard ratio [HR] = 0.69; 1-sided $P = 0.003$) and the safety profile of CPX-351 was consistent with the known profile of the 7+3 regimen[6]

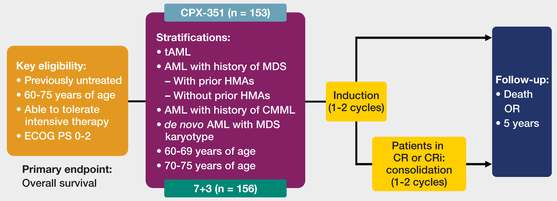
Objective

- To compare the efficacy and safety of CPX-351 versus conventional 7+3 in patients with RAEB-t AML in an exploratory *post hoc* analysis using data from the phase 3 trial

Methods

- Randomized, open-label, controlled, multicenter, phase 3 trial (ClinicalTrials.gov Identifier: NCT01696084)
- Patients randomized 1:1 to receive 1 to 2 induction cycles with CPX-351 or 7+3, stratified by age (60-69 and 70-75 years) and AML subtype
  - CPX-351: 100 units/m^2 (cytarabine 100 mg/m^2 + daunorubicin 44 mg/m^2); 90-minute infusion on Days 1, 3, and 5 (Days 1 and 3 for second induction)
  - 7+3: cytarabine 100 mg/m^2/day continuous infusion for 7 days (5 days for second induction) + daunorubicin 60 mg/m^2 on Days 1, 2, and 3 (Days 1 and 2 for second induction)
- Up to 2 consolidation cycles for patients with complete remission (CR) or CR with incomplete recovery of platelets or neutrophils (CRi)
  - CPX-351: 65 units/m^2 (cytarabine 65 mg/m^2 + daunorubicin 29 mg/m^2); 90-minute infusion on Days 1 and 3
  - 7+3: cytarabine 100 mg/m^2/day continuous infusion for 5 days + daunorubicin 60 mg/m^2 on Days 1 and 2
- Patients could be considered for allogeneic hematopoietic cell transplantation (HCT), based on institutional criteria

Figure 1. Phase 3 Study Design



ECOG PS, Eastern Cooperative Oncology Group performance status; tAML, therapy-related acute myeloid leukemia; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; HMA, hypomethylating agent; CMML, chronic myelomonocytic leukemia; CR, complete remission; CRi, complete remission with incomplete recovery of platelets or neutrophils.

- Key Inclusion Criteria: Adults 60 to 75 years of age; pathologic diagnosis of AML according to World Health Organization 2008 criteria (≥20% blasts in peripheral blood or bone marrow); high-risk/sAML based on prior cytotoxic treatment, history of MDS or chronic myelomonocytic leukemia, or *de novo* AML with cytogenetic changes linked to MDS; ability to tolerate intensive AML chemotherapy
- Key Exclusion Criteria: Acute promyelocytic leukemia t(15;17) or favorable cytogenetics at screening; prior treatment intended as induction therapy for AML (hydroxyurea permitted); active secondary malignancies or central nervous system leukemia

Results

Table 1. Baseline Demographics and Clinical Characteristics for Patients With RAEB-t AML

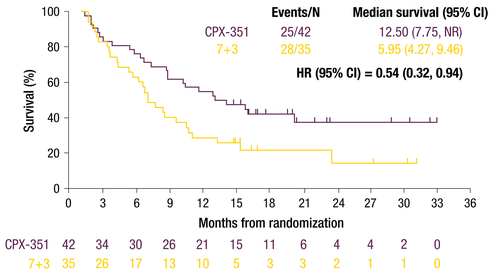
Characteristic, n (%)	CPX-351 (n = 42)	7+3 (n = 35)
Demographic characteristics		
Age		
60-69 years	26 (62)	21 (60)
70-75 years	16 (38)	14 (40)
ECOG PS		
0	14 (33)	10 (29)
1	23 (55)	19 (54)
2	5 (12)	6 (17)
Clinical characteristics		
AML subtype		
de novo AML with MDS karyotype	11 (26)	3 (9)
History of MDS with prior HMA treatment	16 (38)	14 (40)
History of MDS without prior HMA treatment	3 (7)	5 (14)
History of CMML	5 (12)	4 (11)
Therapy-related AML	7 (17)	9 (26)
Cytogenetic risk by NCCN		
Favorable/intermediate	22/41 (54)	20/31 (65)
Unfavorable	19/41 (46)	11/31 (36)
White blood cell count		
<20 × 10^9/L	38 (91)	32 (91)
≥20 × 10^9/L	4 (10)	3 (9)
Platelet count		
≤50 × 10^9/L	24 (57)	22 (63)
>50 × 10^9/L	18 (43)	13 (37)
FLT3 mutation[a]	3/36 (8)	3/30 (10)

RAEB-t, refractory anemia with excess of blasts in transformation; AML, acute myeloid leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; MDS, myelodysplastic syndrome; HMA, hypomethylating agent; CMML, chronic myelomonocytic leukemia; NCCN, National Comprehensive Cancer Network; *FLT3*, FMS-like tyrosine kinase 3.

[a]Included internal tandem duplications and kinase domain mutations.

- Of the 309 patients enrolled in the study, 77 patients met the criteria for RAEB-t AML and were treated with CPX-351 (n = 42) or 7+3 (n = 35)
- Baseline demographics and clinical characteristics were generally well balanced between treatment arms

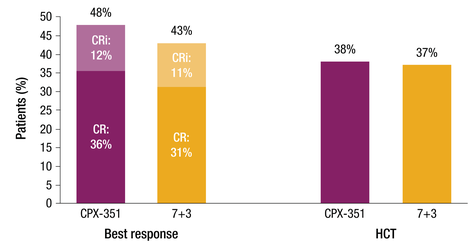
Figure 2. Kaplan-Meier Curve for OS in Patients With RAEB-t AML



OS, overall survival; RAEB-t, refractory anemia with excess of blasts in transformation; AML, acute myeloid leukemia; CI, confidence interval; NR, not reached; HR, hazard ratio.

- Consistent with the overall study population, an OS benefit was observed with CPX-351 versus 7+3 among patients with RAEB-t AML
  - Kaplan-Meier–estimated 2-year OS rates were 37% with CPX-351 and 14% with 7+3
- Among patients with RAEB-t AML previously treated with HMAs (CPX-351: n = 20/42 [48%]; 7+3: n = 20/35 [57%]), median OS was prolonged with CPX-351 versus 7+3 (8.54 vs 5.95 months; HR [95% confidence interval] = 0.53 [0.26, 1.09])

Figure 3. Best Response and HCT Rates in Patients With RAEB-t AML[a]



HCT, hematopoietic cell transplantation; RAEB-t, refractory anemia with excess of blasts in transformation; AML, acute myeloid leukemia; CRi, complete remission with incomplete recovery of platelets or neutrophils; CR, complete remission.

[a]Differences in best response and HCT rates were not significant for this subpopulation.

- In the RAEB-t subgroup, 16 (38%) patients treated with CPX-351 and 13 (37%) patients treated with 7+3 underwent HCT, including 7 with CR and 3 with CRi at transplant in the CPX-351 arm, and 6 with CR and 2 with CRi at transplant in the 7+3 arm
  - Median OS, landmarked from HCT, was not reached with CPX-351 and was 6.28 months with 7+3 (HR [95% confidence interval] = 0.20 [0.05, 0.77])

Table 2. Summary of TEAEs in Patients With RAEB-t AML

Safety parameter, n (%)	CPX-351 (n = 42)	7+3 (n = 35)
TEAEs reported in ≥25% of patients in either treatment arm		
Febrile neutropenia	28 (67)	27 (82)
Nausea	25 (60)	19 (58)
Diarrhea	18 (43)	23 (70)
Fatigue	17 (40)	12 (36)
Headache	17 (40)	8 (24)
Cough	16 (38)	9 (27)
Peripheral edema	15 (36)	20 (61)
Vomiting	15 (36)	8 (24)
Chills	14 (33)	12 (36)
Epistaxis	14 (33)	6 (18)
Abdominal pain	11 (26)	3 (9)
Constipation	11 (26)	9 (27)
Decreased appetite	11 (26)	11 (33)
Hypotension	11 (26)	10 (30)
Rash	10 (24)	9 (27)
Mucosal inflammation	6 (14)	9 (27)
Grade 3 or 4 TEAE	37 (88)	32 (97)
Serious TEAE	18 (43)	11 (33)
Discontinuation due to a TEAE	0	0
TEAE leading to death	4 (10)	5 (15)

TEAE, treatment-emergent adverse event; RAEB-t, refractory anemia with excess of blasts in transformation; AML, acute myeloid leukemia.

- Among patients with RAEB-t AML, early mortality rates were 10% and 9% at Day 30 in the CPX-351 and 7+3 arms, respectively, and 17% and 18% at Day 60
- The most frequently reported serious TEAEs in the RAEB-t AML subgroup were febrile neutropenia (CPX-351: n = 3 [7%]; 7+3: n = 1 [3%]), disease progression (CPX-351: n = 1 [2%]; 7+3: n = 2 [6%]), and ejection fraction decreased (CPX-351: n = 1 [2%]; 7+3: n = 2 [6%])
- Disease progression (CPX-351: n = 1 [2%]; 7+3: n = 2 [6%]) was the only grade 5 TEAE reported for >1 patient in the RAEB-t AML subgroup

Conclusions

- Survival was superior with CPX-351 compared with 7+3 in older adults with newly diagnosed RAEB-t AML and high-risk disease features, both overall and among patients who underwent HCT
- The safety profile of CPX-351 was comparable to that of 7+3 in patients with RAEB-t AML and consistent with the overall phase 3 study population,[6] as well as other reports of CPX-351 in high-risk AML subpopulations[7,8]
- Although this analysis was limited by the small subpopulation of patients with RAEB-t AML enrolled in the phase 3 study, these results suggest that CPX-351 should be explored further in related disease groups, including high-risk MDS

References: 1. Pleyer L, et al. *J Hematol Oncol.* 2016;9:39. **2.** Estey E, et al. *Blood.* 1997;90(8):2969-2977. **3.** Maurillo L, et al. *Mediterr J Hematol Infect Dis.* 2013;5(1):e2013032. **4.** VYXEOS™ (daunorubicin and cytarabine injection), solution for intravenous use [package insert]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; 2017. **5.** Jazz Pharmaceuticals [press release]. Dublin, Ireland; August 27, 2018. **6.** Lancet JE, et al. *J Clin Oncol.* 2018;36(26):2684-2692. **7.** Lancet JE, et al. *Blood.* 2014;123(21):3239-3246. **8.** Cortes JE, et al. *Cancer.* 2015;121(2):234-242.

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