CPX-351 (Cytarabine:Daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukemia

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1. **Exploratory subgroup analyses**

Exploratory analyses were performed to investigate the effect of demographic and baseline clinical characteristics on OS. The exploratory analyses by age group and AML subtype were prespecified; other subgroup evaluations were *post hoc* analyses. Median OS was significantly improved with CPX-351 versus 7+3 irrespective of age and in patients with wild-type *FLT3*, therapy-related AML, AML with antecedent MDS or CMML, and favorable/intermediate cytogenetic risk classification; trends for improved OS were also seen in patients with baseline *FLT3* mutations, *de novo* AML with MDS-related cytogenetic abnormalities, and unfavorable cytogenetic risk (**Fig 3**).

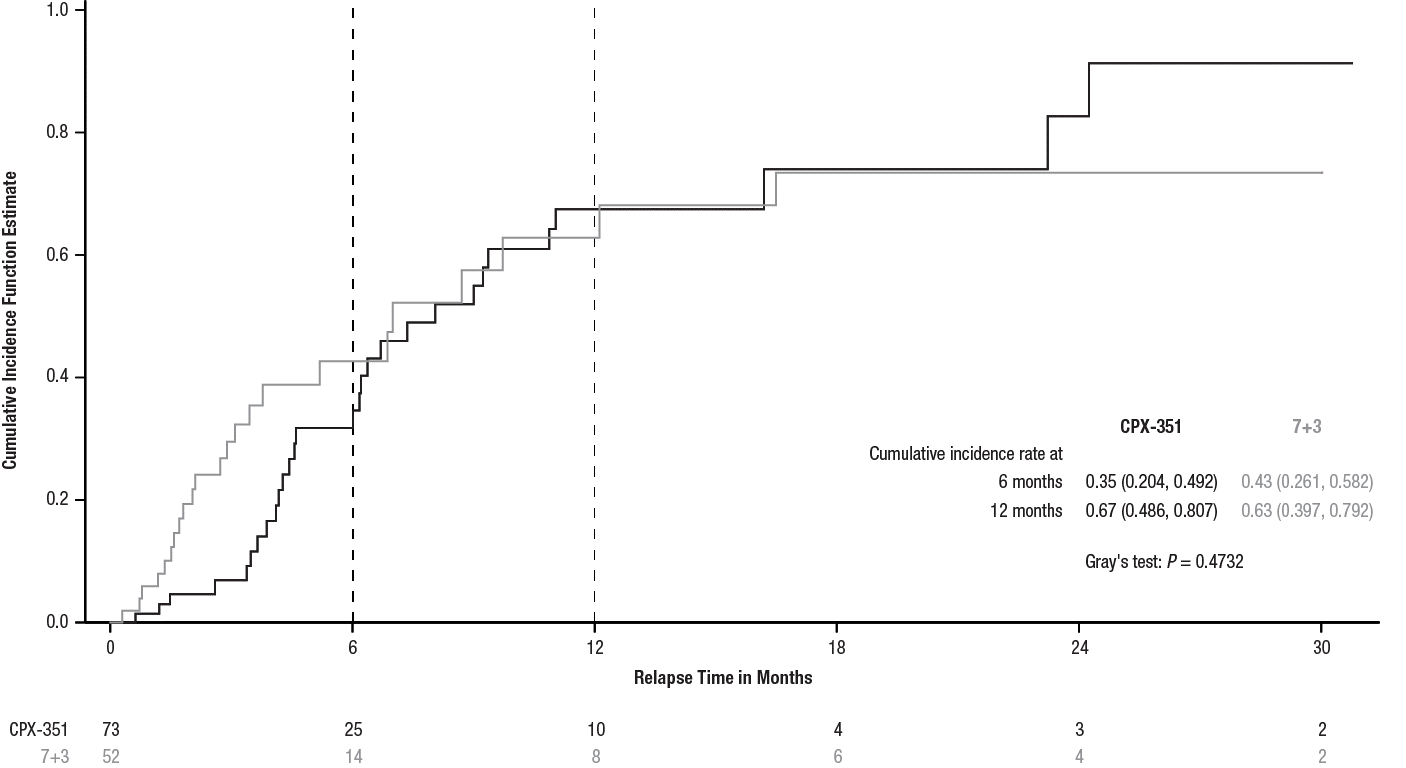
Although no differences in OS by male/female sex were seen in prespecified univariate and multivariate analyses (**Appendix** **Table S1 and S2**), an exploratory *post hoc* analysis suggested a difference in OS with CPX-351 between males (median OS: 10.09 months with CPX-351 *v* 5.55 months with 7+3; HR, 0.50 [95% CI, 0.35 to 0.71]) and females (median OS: 7.59 months with CPX-351 *v* 7.21 months with 7+3; HR, 0.96 [95% CI, 0.61 to 1.53]). The difference is likely due to a multiplicity problem that arises out of multiple comparisons between the treatment groups without controlling for type I error. Additionally, because only 38.5% of the study population were female, this *post hoc* analysis was likely underpowered. There appear to be some differences in patient demographic and baseline clinical characteristics between male and female patients in this study (**Table S5**), and thus it is not meaningful to compare these subgroups in terms of efficacy. In a separate CPX-351 population pharmacokinetic analysis of 195 patients with acute leukemia or myelodysplastic syndrome, prespecified covariate analyses indicated that sex does not appear to account for significant sources of variability in the pharmacokinetic parameters for total cytarabine or daunorubicin (data on file, Jazz Pharmaceuticals, Inc., VYX-2017-0044). To further investigate the effect of sex on OS benefit with CPX-351, data from the prior phase II studies of CPX-351 in adults with newly diagnosed AML1 or relapsed/refractory AML2 were also analyzed. Although neither study was designed to show a difference in OS by patient sex, median survival was longer in the CPX-351 arms for males and females in both studies (data on file, Jazz Pharmaceuticals, Inc., VYX-2017-045). Thus, CPX-351 is expected to provide a survival benefit for both men and women.

Of note, a similar phenomenon of greater OS benefit seen in male versus female patients was reported for a phase III study of midostaurin in combination with cytarabine and daunorubicin in adults aged 18-59 years with newly diagnosed AML with a *FLT3* mutation.3 Similar to our study, the authors of the midostaurin publication could find no obvious explanation for the difference in OS benefit between sexes in their study, and they noted that prior studies of midostaurin had not suggested a pharmacokinetic difference between men and women.3

**References**

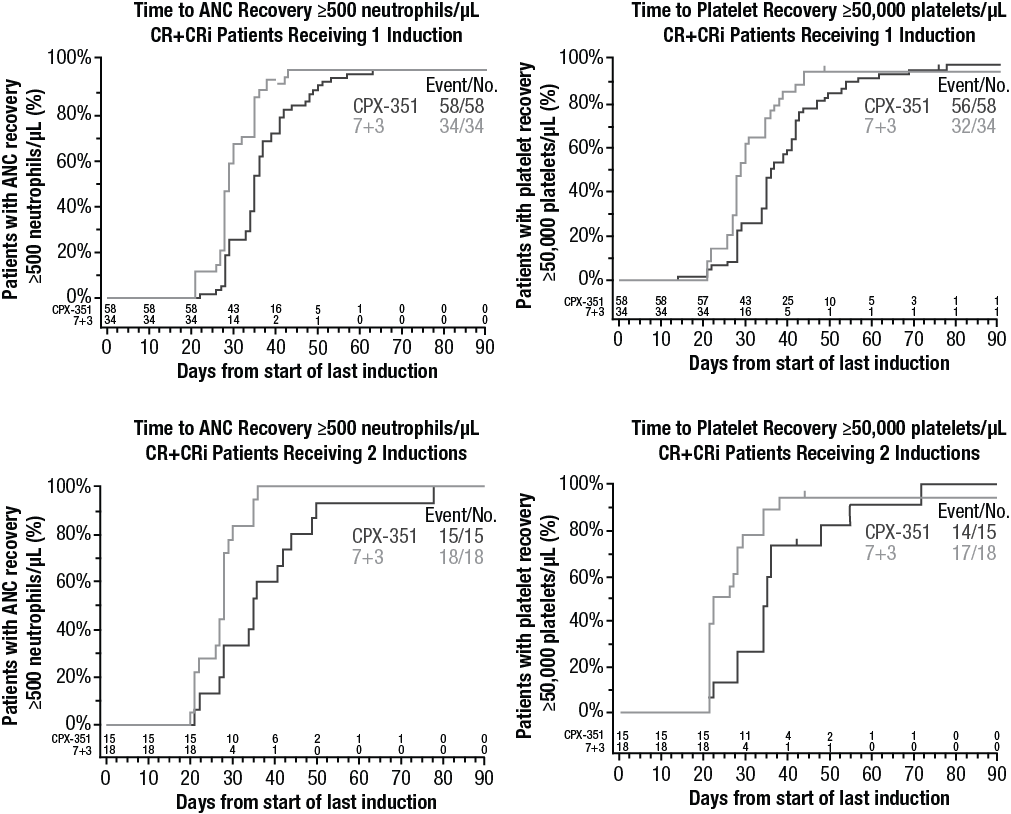
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2. Cortes JE, Goldberg SL, Feldman EJ, et al: Phase II, multicenter, randomized trial of CPX-351 (cytarabine:daunorubicin) liposome injection versus intensive salvage therapy in adults with first relapse AML. Cancer 121:234-242, 2015
3. Stone RM, Mandrekar SJ, Sanford BL, et al: Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med 377:454-464, 2017
4. **Supplemental figures**

**Fig S1.** Kaplan-Meier curve of cumulative incidence of relapse for patients achieving CR or CRi.

Cumulative incidence of relapse was calculated for patients who achieved CR+CRi. Events included relapsed from CR+CRi and death; patients were censored at time of HCT. Among patients who achieved CR+CRi, the cumulative incidence of relapse at 6 months was 0.35 in the CPX-351 arm and 0.43 in the 7+3 arm, and at 1 year was 0.67 in the CPX-351 arm and 0.63 in the 7+3 arm; values are shown with their 95% confidence intervals in the figure. Among patients with CR+CRi, 26.0% and 26.9% of patients in the CPX-351 and 7+3 cohorts had relapsed at 1 year, respectively. CR, complete remission; CRi, CR with incomplete neutrophil or platelet count recovery; HCT, hematopoietic cell transplantation. ******

**Fig S2.** Complete recovery counts for patients achieving CR or CRi.

Median time to neutrophil recovery (≥500/µL) was longer after induction with CPX-351 than with 7+3 (initial induction: 35 *v* 29 days; second induction: 35 *v* 28 days). Similarly, median time to platelet recovery (≥50,000/µL) was longer following CPX-351 than 7+3 (initial induction: 36.5 *v* 29 days; second induction: 35 *v* 24 days). CR, complete remission; CRi, CR with incomplete neutrophil or platelet count recovery; ANC, absolute neutrophil count.



1. **Supplemental tables**

**Table S1.** Univariate Cox Regression Analysis for OS

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Factor** | **Factor level** | **no./No. (%)** | **Hazard ratio (95% CI)** | **Overall *P* value** |
| Sex | Male  Female | 190/309 (61.5)  119/309 (38.5) | 1.02 (0.78 to 1.34) | 0.892 |
| ECOG PS | 0  1  2 | 82/309 (26.5)  190/309 (61.5)  37/309 (12.0) | 0.44 (0.28 to 0.69)  0.65 (0.44 to 0.96) | 0.001 |
| Karyotype | Non-adverse  Adverse | 134/289 (46.4)  155/289 (53.6) | 0.42 (0.31 to 0.58) | <0.001 |
| WBC | <20×109/L  ≥20×109/L | 262/308 (85.1)  46/308 (14.9) | 0.53 (0.37 to 0.75) | <0.001 |
| Platelets | ≤50×109/L  >50×109/L | 186/307 (60.6)  121/307 (39.4) | 1.55 (1.17 to 2.05) | 0.002 |
| Hemoglobin | ≤9 g/dL  >9 g/dL | 206/308 (66.9)  102/308 (33.1) | 1.26 (0.94 to 1.68) | 0.122 |
| Bone marrow blast percentage | <20%  20%-40%  >40%-60%  >60% | 43/299 (14.4)  127/299 (42.5)  68/299 (22.7)  61/299 (20.4) | 0.57 (0.35 to 0.90)  0.67 (0.47 to 0.96)  0.70 (0.47 to 1.04) | 0.071 |
| *FLT3*-ITD mutation | No  Yes | 246/280 (87.9)  34/280 (12.1) | 0.74 (0.49 to 1.12) | 0.155 |
| Treatment arm | CPX-351  7+3 | 153/309 (49.5)  156/309 (50.5) | 0.69 (0.52 to 0.90) | 0.006 |

Abbreviations: OS, overall survival; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; *FLT3*, FMS-like tyrosine kinase 3; ITD, internal tandem duplication mutation; WBC, white blood cell count.

The last factor level listed is the reference level for the associated hazard ratios; *P* values were calculated from the Wald chi-square test.

**Table S2.** Multivariate Cox Regression Analysis for OS

| **Factor** | **Factor level** | **no./No. (%)** | | | **Hazard ratio (95% CI)** | **Overall *P* value** |
| --- | --- | --- | --- | --- | --- | --- |
| ECOG PS | 0  1  2 | | 72/287 (25.1)  180/287 (62.7)  35/287 (12.2) | 0.53 (0.33 to 0.86)  0.73 (0.48 to 1.10) | | 0.034 |
| Karyotype | Non-adverse  Adverse | | 133/287 (46.3) 154/287 (53.7) | 0.47 (0.34 to 0.65) | | <0.001 |
| WBC | <20×109/L  ≥20×109/L | | 246/287 (85.7) 41/287 (14.3) | 0.67 (0.45 to 0.98) | | 0.041 |
| Platelets | ≤50×109/L  >50×109/L | | 174/287 (60.6)  113/287 (39.4) | 1.66 (1.24 to 2.24) | | <0.001 |
| Treatment arm | CPX-351  7+3 | | 143/287 (49.8)  144/287 (50.2) | 0.68 (0.51 to 0.90) | | 0.008 |

Abbreviations: OS, overall survival; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; WBC, white blood cell count.

The last factor level listed is the reference level for the associated hazard ratios; *P* values were calculated from the Wald chi-square test.

**Table S3.** Demographic and Baseline Clinical Characteristics of Patients Who Underwent Allogeneic HCT

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Aged 60-69 years** | | **Aged 70-75 years** | |
| **Characteristic** | **CPX-351**  **(n = 36)** | **7+3**  **(n = 33)** | **CPX-351**  **(n = 16)** | **7+3**  **(n = 6)** |
| Sex, no. (%) |  |  |  |  |
| Male | 21 (58) | 18 (55) | 12 (75) | 5 (83) |
| Female | 15 (42) | 15 (45) | 4 (25) | 1 (17) |
| Race, no. (%) |  |  |  |  |
| White | 28 (78) | 27 (82) | 16 (100) | 5 (83) |
| Black or African American | 0 | 3 (9) | 0 | 1 (17) |
| Asian | 5 (14) | 1 (3) | 0 | 0 |
| American Indian or Alaska Native | 0 | 0 | 0 | 0 |
| Other | 3 (8) | 2 (6) | 0 | 0 |
| ECOG PS, no. (%) |  |  |  |  |
| 0 | 11 (31) | 15 (45) | 7 (44) | 2 (33) |
| 1 | 23 (64) | 16 (48) | 7 (44) | 4 (67) |
| 2 | 2 (6) | 2 (6) | 2 (13) | 0 |
| AML subtype, no. (%) |  |  |  |  |
| Therapy-related AML | 6 (17) | 8 (24) | 5 (31) | 1 (17) |
| AML with antecedent MDS | 17 (47) | 16 (48) | 4 (25) | 3 (50) |
| With prior HMA | 13 (36) | 12 (36) | 1 (6) | 2 (33) |
| Without prior HMA | 4 (11) | 4 (12) | 3 (19) | 1 (17) |
| AML with antecedent CMML | 0 | 0 | 3 (19) | 0 |
| *de novo* AML with MDS karyotype | 13 (36) | 9 (27) | 4 (25) | 2 (33) |

Abbreviations: HCT, hematopoietic stem cell transplantation; ECOG PS, Eastern Cooperative Oncology Group performance status; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; HMA, hypomethylating agent; CMML, chronic myelomonocytic leukemia.

**Table S4**. Causes of Death by Treatment Arm

|  |  |  |
| --- | --- | --- |
|  | **CPX-351**  **(N = 153)** | **7+3 (N = 156)** |
| Overall deaths, no. (%) | 106 (69.3) | 128 (84.8) |
| Progressive leukemia | 65 | 67 |
| Adverse event | 15 | 19 |
| Non-progressive disease cancer-related organ failure | 0 | 5 |
| Unknown/other | 26 | 37 |
| Death within 30 days of treatment start, no. | 9 | 16 |
| Death within 60 days of treatment start, no. | 21 | 32 |

**Table S5.** Demographic and Baseline Clinical Characteristics of Male and Female Patients

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristic** | **CPX-351** | | **7+3** | |
| **Male**  **(n = 94)** | **Female**  **(n = 59)** | **Male**  **(n = 96)** | **Female**  **(n = 60)** |
| Age |  |  |  |  |
| Mean (SD), years | 67.7 (4.18) | 67.8 (4.25) | 68.2 (4.12) | 66.9 (3.98) |
| 60-69 years, no. (%) | 59 (63) | 37 (63) | 58 (60) | 44 (73) |
| 70-75 years, no. (%) | 35 (37) | 22 (37) | 38 (40) | 16 (27) |
| Race, no. (%) |  |  |  |  |
| White | 81 (86) | 47 (80) | 86 (90) | 53 (88) |
| Black or African American | 4 (4) | 3 (5) | 3 (3) | 3 (5) |
| Asian | 2 (2) | 4 (7) | 1 (1) | 1 (2) |
| Other | 7 (8) | 5 (8) | 6 (6) | 3 (5) |
| ECOG PS, no. (%) |  |  |  |  |
| 0 | 21 (22) | 16 (27) | 28 (29) | 17 (28) |
| 1 | 68 (72) | 33 (56) | 55 (57) | 34 (57) |
| 2 | 5 (5) | 10 (17) | 13 (14) | 9 (15) |
| AML subtype, no. (%) |  |  |  |  |
| Therapy-related AML | 14 (15) | 16 (27) | 17 (18) | 16 (27) |
| AML with antecedent MDS | 43 (46) | 28 (47) | 53 (55) | 21 (35) |
| With prior HMA | 32 (34) | 18 (31) | 38 (40) | 17 (28) |
| Without prior HMA | 11 (12) | 10 (17) | 15 (16) | 4 (7) |
| AML with antecedent CMML | 10 (11) | 1 (2) | 6 (6) | 6 (10) |
| *de novo* AML with MDS karyotype | 27 (29) | 14 (24) | 20 (21) | 17 (28) |
| Cytogenetic risk by NCCN, no. (%) |  |  |  |  |
| Favorable | 4 (4) | 3 (6) | 3 (3) | 2 (4) |
| Intermediate | 47 (53) | 17 (31) | 40 (45) | 18 (32) |
| Unfavorable | 38 (43) | 34 (63) | 46 (52) | 37 (65) |
| Median % (range) bone marrow blasts (aspirate) | 35.0 (5-87) | 36.5 (8-93) | 35.0 (3-97) | 35.0 (6-90) |
| WBC, no. (%) |  |  |  |  |
| <20×109/L | 80 (85) | 51 (86) | 76 (80) | 55 (92) |
| ≥20×109/L | 14 (15) | 8 (14) | 19 (20) | 5 (8) |
| *FLT3* mutation, no. (%) | 12 (14) | 10 (20) | 14 (16) | 7 (13) |

Abbreviations: SD, standard deviation; ECOG PS, Eastern Cooperative Oncology Group performance status; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; HMA, hypomethylating agent; CMML, chronic myelomonocytic leukemia; NCCN, National Comprehensive Cancer Network; WBC, white blood cell count; *FLT3*, FMS-like tyrosine kinase 3.