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Letter to *Blood*

TO THE EDITOR:

Safety and efficacy of CPX-351 in younger patients (<60 years old) with secondary acute myeloid leukemia

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Patients with secondary acute myeloid leukemia (s-AML), a category which includes AML with myelodysplasia-related changes (AML-MRC) and treatment-related AML (t-AML), have poor long-term outcomes following standard induction chemotherapy ("7+3").[1,2] A previous population-based study demonstrated median survival of 6 to 7 months for patients with s-AML and 8 to 14 months for those with t-AML.[1] In 2017, a liposomal cytarabine and daunorubicin formulation (CPX-351) was Food and Drug Administration (FDA) approved for upfront treatment of s-AML based on a pivotal phase 3 trial demonstrating improved overall survival (OS) (9.56 vs 5.95 months; hazard ratio [HR], 0.69; 95% confidence interval [CI], 0.52-0.9) and remission rates (complete remission [CR]/CR with incomplete count recovery [CRi]) (47.7% vs 33.3%; P = .016) in patients aged 60 to 75 years old than induction chemotherapy with "7+3."[3] The benefits from therapy with CPX-351 were retained at the 5-year time point as well with median OS of 9.33 vs 5.95 months with "7+3."[4] CPX-351 treatment was subsequently approved for s-AML regardless of age. Here, we present safety and efficacy data in patients younger than 60 years old who were not eligible to be treated on this study. We sought to address the paucity of such data by retrospective review of clinical experience since FDA approval at 6 large academic centers.

Medical records were reviewed at each institute to identify all patients aged 18 to 59 years old with untreated s-AML defined as AML evolving from antecedent myelodysplastic syndromes (MDS) or chronic myelomonocytic leukemia (CMML), AML arising from previous cytotoxic or radiation therapy, or AML with World Health Organization–defined myelodysplasia-related changes (AML-MRC) treated with CPX-351 as induction therapy from August 2017 to December 2021. Variables including demographics, disease-specific variables, and outcomes were collected in accordance with the Roswell Park Institutional Review Board approved protocol and the Declaration of Helsinki. Responses to therapy were defined per 2003 International Working Group criteria,[5] and comparison between groups was made using Fisher exact test (SPSS 28.0.1). Kaplan-Meier method was used to estimate the distribution of events over time. Time-to-events were evaluated using a stratified log-rank test to compare treatment groups. HRs and 95% CIs were estimated using a Cox proportional hazard model. GraphPad Prism, version 9.2.0 (GraphPad, La Jolla, CA) was used for statistical analysis.

A total of 66 patients with confirmed s-AML or t-AML treated with CPX-351 were included in this study. Median age was 54.9 years (range, 23-59), and 37 (56%) were male. The majority (N = 52, 79%) of patients had AML-MRC, and 14 (21%) had t-AML. Of the 66 patients, 16 had received previous hypomethylating therapy (HMA) for antecedent MDS. Cytogenetics were complex in 30 (46%), monosomal in 17 (26%), normal in 10 (15%), −7 in 7 (11%), +8 in 4 (6%), −17p in 3 (5%), and −5q in 2 (3%) patients. The most common mutations were *TP53* (29%), *RUNX1* (21%), *DNMT3A* (17%), *NRAS* (17%), *ASXL1* (11%), and *NPM1* (11%) (Table 1; supplemental Table 1, available on the *Blood* website).

Most patients (N = 59, 89%) received one cycle of CPX-351 induction; 7 received 2 cycles (11%) (supplemental Table 2). At the time of analysis, response assessment was available for 62 patients. The overall complete response (CR/CRi) rate was 43.5% including 19 CR (30.6%) and 8 CR with incomplete count recovery (CRi, 12.9%). Two patients (3.2%) obtained morphologic leukemia-free state (MLFS) and the remainder (N = 33, 53%) did not respond (Table 1). Median duration of response from CR/CRi was 5.3 months (range, 0.5-14.2 months). A total of 31 patients (31/66, 47%) proceeded onto hematopoietic stem cell transplant (HSCT) after a median of 2 cycles within a median of 2.8 months. The CR/CRi rate among evaluable patients with *TP53* mutated (*TP53*mut) AML was 31.6% (6/19), compared with 48.8% (21/41) in patients with *TP53* wild type (*TP53*wt) (P = .26). However, median duration of remission was similar for patients with *TP53*wt and *TP53*mut (5.2 vs 5.4 months; P = .84). Patients with previous HMA exposure had a CR/CRi of 25% (4/16) vs

Table 1. Patient characteristics and outcomes

Characteristics	N (%)
Total patients	66 (100)
Age, median (range) (y)	54.9 (23-59)
Gender	
Male	37 (56)
Female	29 (44)
AML subtype	
AML-MRC	52 (79)
Morphology	17 (26)
Cytogenetics	11 (17)
Prior Dx MDS	23 (35)
Prior Dx CMML	1 (2)
Therapy-related AML	14 (21)
Previous HMA treatment for MDS	
Yes	16 (24)
No	50 (76)
Baseline mutations of interest	
TP53	19 (30)
RUNX1	14 (22)
DNMT3A	11 (17)
NRAS	11 (17)
ASXL1	7 (11)
NPM1	7 (11)
FLT3 ITD	5 (8)
IDH1	5 (8)
IDH2	3 (5)
Cytogenetics	
Complex	30 (46)
Monosomal	17 (26)
Normal	10 (15)
Del 7	7 (11)
Trisomy 8	4 (16)
17p	3 (5)
Minus 5q	2 (3)
Outcomes (out of 62 pts)	
CR	19 (30.6)
CRi	8 (12.9)
CR/CRi	27 (43.5)
MLFS	2 (3.2)
NR	33 (53)
Mortality	
30 d	6 (9.1)
60 d	11 (16.7)

Dx, diagnosis; pts, patients; NR, nonresponder.

patients who were HMA naïve (CR/CRi, 50%; P = .15) (supplemental Table 3).

With a median follow-up of 12.4 months, the median OS in all 66 patients was 12.2 months (range, 0.2-36.2 months) (Figure 1A). In addition, landmark analysis of OS in 31 patients who underwent HSCT calculated from the time of transplantation demonstrated a median OS that was not reached (range, 2.3-34.1 months) (Figure 1B). Event-free survival (EFS) for all patients was not reached (range, 0.5-14.2 months) (Figure 1C). When stratifying for *TP53*mut, there were no differences in OS (median, 13.6 vs 8.6 months; P = .4) based on *TP53* status (Figure 1D). In addition, we observed similar OS in patients who were HMA naïve and HMA exposed (10.2 vs 12.2 months; P = .8) (Figure 1E). Median time to count recovery was 37.2 and 39.8 days for neutrophils and platelets, respectively (supplemental Table 4). The most common adverse events included neutropenic fever (29/43, 67.4%) and 4 reports (9.3%) of clinically significant bleeding (supplemental Table 5). Early mortality was 9.1% at 30 days, and 16.7% at 60 days.

Overall, this multi-institutional retrospective analysis demonstrates comparable response rates (CR/CRi, 43.5%) and OS (12.2 months) for CPX-351 in younger patients (<60 years old) than older individuals in the phase 3 study (CR/CRi, 47.7%; median OS, 9.56 months) (Table 1).[3] The majority (79%) of younger patients had a diagnosis of AML-MRC. These outcomes suggest the underlying biology of s-AML impacts outcome more than age. Despite lower CR/CRi rates in *TP53* mutant AML and in patients with previous HMA, OS for patients were similar regardless of *TP53* status or previous therapy. Historically, patients <65 years old with s-AML had a reported OS of approximately 7 months. Our data demonstrate that CPX-351 followed by HSCT may improve outcomes of younger patients with s-AML as compared with previous studies.

The authors acknowledge that as a retrospective study other unaccounted factors may contribute to our observed OS. To date, HSCT has been a mainstay of therapy for patients with s-AML, offering the only curative option.[6-10] This is supported by our landmark OS analysis where median OS was not reached among those who went to transplant. Consistent with our observation, Matthews and colleagues evaluated real-world outcomes for patients with AML induced with CPX-351 or azacitidine/venetoclax.[11] They demonstrated superior survival in those who underwent HSCT irrespective of induction strategy. This work highlights the crucial role of consolidation with HSCT in this patient population following the achievement of therapeutic response to chemotherapy. However, lack of response following CPX-351 in patients with previous HMA exposure (69%) or *TP53* mutation (63%) preclude HSCT; for these individuals, clinical trials of agents such as venetoclax, eprenetapopt, magrolimab, or other immunotherapy remain a high priority.

The authors acknowledge that this study is limited by the small number of patients, retrospective study design, and short duration of follow-up. A phase II study prospectively evaluating CPX-351 in patients <60 years old with s-AML is ongoing and

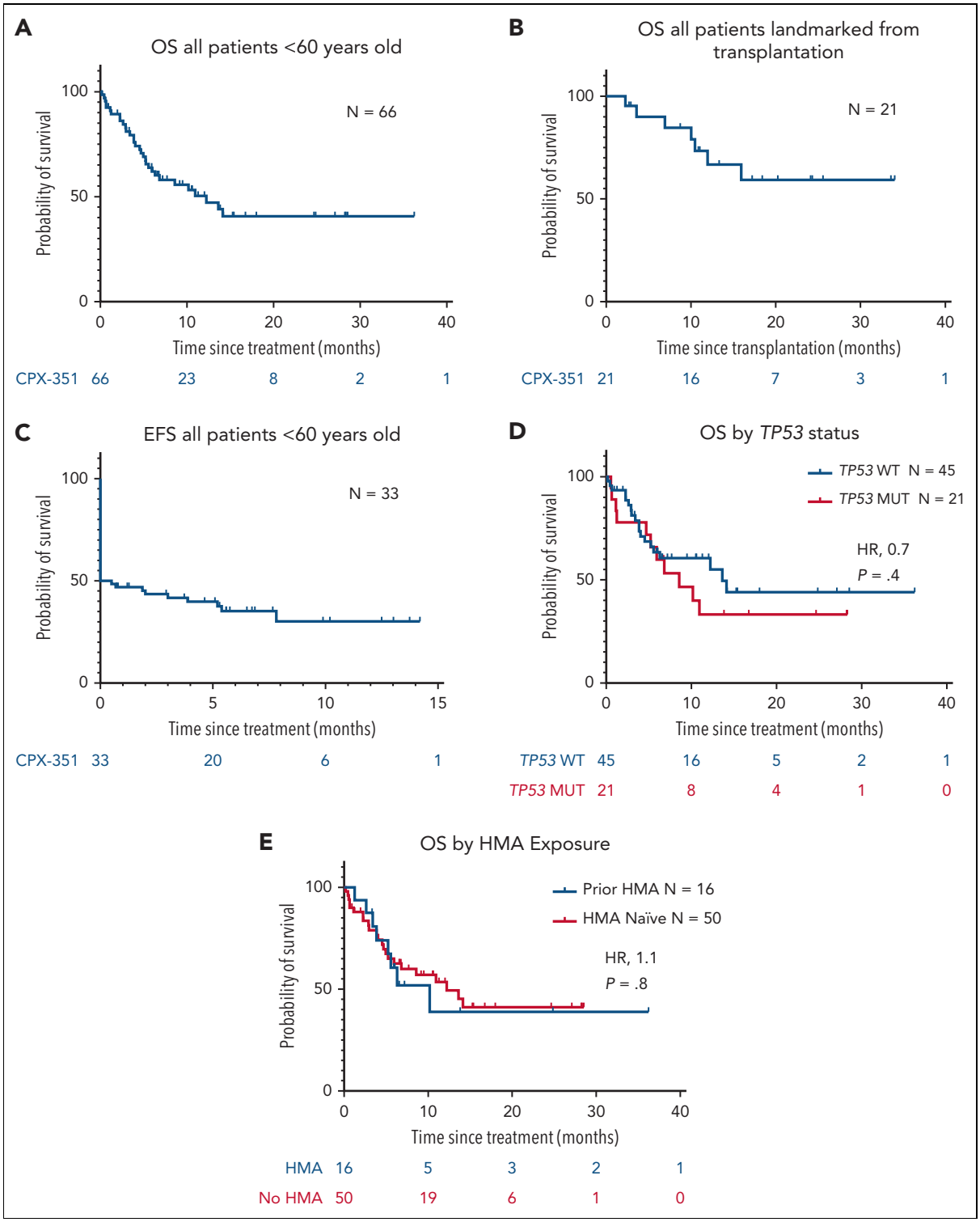

Figure 1. Kaplan-Meier estimates of median OS and EFS. (A) Median OS for all patients was found to be 12.2 months (range, 0.2-36.2 months). (B) Median OS landmarked from the date of transplantation was NR (range, 2.3-34.1 months). (C) Median EFS for all patients was NR (range, 0.5-14.2 months). (D) Median OS of patients with *TP53*wt vs *TP53*mut (13.6 vs 8.6 months). (E) Median OS of patients naïve to hypomethylating therapy (HMA) vs patients exposed to HMA (10.2 vs 12.2 months).

open to accrual (NCT04269213). Although such patients are traditionally considered better risk than their older counterparts considering their "youth" and fitness for intensive chemotherapy, our study highlights the poor survival outcome in younger patients with s-AML who are unable to proceed to HSCT. Although our data show somewhat improved outcomes for young patients with s-AML bridged to HSCT with CPX-351, overall outcomes in this high-risk population remain sobering and emphasize the need to accelerate development of novel therapeutic approaches.

Patients provided written informed consent for therapy with CPX-351, and the research was conducted in accordance with the Roswell Park Comprehensive Cancer Center Institutional Review Board approved protocol and the Declaration of Helsinki.

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Authorship

Contribution: A.P. and E.S.W. designed and conceived the study; A.P., A.D.G., C.T., S.F., P.V., S.S., J.W., B.B., C.F., and M.S. identified patients and performed clinical annotation; A.P., A.D.G., S.F., P.V., S.T., J.B., E.A.G., J.E.T., K.S., and E.S.W. analyzed and interpreted the data; and A.P. and E.S.W. wrote the manuscript with assistance from all other authors.

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Footnotes

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Data are available on request from the corresponding author, Amanda Przespolewski (amanda.przespolewski@roswellpark.org).

The online version of this article contains a data supplement.

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