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A randomized comparison of CPX-351 and FLAG-Ida in high-risk myelodysplastic syndrome: A subgroup analysis of UK NCRI AML19

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Keywords: CPX-351; hematopoietic cell transplant; myelodysplastic syndrome; UK NCRI AML19

Highlights:

- CPX-351 ~~showed~~ was associated with a survival advantage versus FLAG-Ida in high-risk MDS
- CPX-351 prolonged relapse-free survival compared with FLAG-Ida
- Fewer serious adverse events occurred with CPX-351 treatment
- Findings ~~support~~ suggest CPX-351 ~~as may be~~ a promising frontline option for high-risk MDS
- Results address an evidence gap in randomized studies of high-risk MDS

Abstract

CPX-351 improves outcomes for patients with secondary acute myeloid leukemia, but evidence of its use in high-risk myelodysplastic syndromes (MDS) is limited. This exploratory subgroup analysis of the randomized, controlled, open-label, phase 3 study—UK NCRI AML19—compared outcomes with CPX-351 versus FLAG-Ida in patients with high-risk MDS, to provide insights into the potential role of CPX-351 in this population. A total of 57 patients were included (CPX-351, n=34; FLAG-Ida, n=23). Compared with FLAG-Ida, CPX-351 prolonged median overall survival (OS; 17.8 vs 10.8 months) and median relapse-free survival (19.1 vs 7 months). Hematopoietic cell transplantation (HCT) rate was 59% and 52% for CPX-351 and FLAG-Ida, respectively. Median OS post-HCT was longer with CPX-351 than FLAG-Ida (22.3 vs 11.6 months). CPX-351 had a lower rate of serious adverse events than FLAG-Ida (9% vs 61%). These findings suggest that CPX-351 may be a promising frontline treatment option for high-risk MDS, and warrant confirmation in prospective studies.

Introduction

Myelodysplastic syndrome (MDS) is a heterogeneous group of myeloid malignancies characterized by bone marrow dysplasia, hematopoiesis failure, peripheral cytopenias, and risk of transformation to acute myeloid leukemia (AML) ¹⁻⁵. To guide therapeutic decision making, MDS is stratified by risk using the Revised International Prognostic Scoring System (IPSS-R) into low- (score ≤ 3.5) and high- (>3.5) risk categories ^{2,3,5}. Patients with high-risk MDS have an overall poor prognosis and elevated risk of progression to AML ^{1,2}. The only curative treatment for high-risk MDS is allogeneic hematopoietic cell transplant (HCT) ². For patients ineligible for HCT, the standard-of-care treatment is limited to hypomethylating agents ^{2,6}. Novel induction strategies are required to increase the proportion of patients receiving HCT and improve post-HCT survival ⁶.

CPX-351, a dual-drug liposomal encapsulation of daunorubicin and cytarabine in a synergistic 1:5 molar ratio, is approved for newly diagnosed secondary AML (sAML), therapy-related AML, or AML with myelodysplasia-related changes in adult and pediatric (aged ≥ 1 year) patients in the US and in adults in the EU/UK ⁷⁻⁹. These approvals were based on the primary analysis of the pivotal phase 3 trial (NCT01696084) that reported a significant overall survival (OS) benefit after a median follow-up of 20.7 months with CPX-351 vs conventional 7+3 chemotherapy in older adults with high-risk/sAML (hazard ratio [HR] 0.69; 95% confidence interval [CI]: 0.52–0.90) ⁹⁻¹¹. Five-year follow-up analysis demonstrated that the OS benefit with CPX-351 vs conventional 7+3 chemotherapy was maintained (median OS: 9.33 months vs 5.95 months; HR 0.70; 95% CI: 0.55–0.91) ¹².

As high-risk MDS shares characteristics with sAML, a recent phase 2, single-arm study (NCT04273802) explored the effectiveness and safety of CPX-351 in 31 patients with high-risk MDS ¹³. Treatment with CPX-351 yielded an overall response rate (ORR) of 87% and no patients died or required intensive care management during induction, allowing bridging to HCT for most patients ¹³. Building upon these results, the randomized, controlled, open-label, phase 3 study, UK NCRI AML19 (ISRCTN78449203), compared the efficacy and safety of CPX-351 with fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin (FLAG-Ida) in a high-risk cohort of younger adults (median age 56 years) with newly diagnosed adverse cytogenetic AML or high-risk MDS ⁶. While the adverse karyotype randomization was not prospectively powered in the original study design and no difference

in OS or event-free survival (EFS) between treatment arms was observed, median relapse-free survival (RFS) in patients achieving complete response (CR) was longer with CPX-351 than FLAG-Ida (22.1 months vs 8.35 months; HR 0.66; 95% CI: 0.41–1.06; $P=0.08$)⁶.

This exploratory subgroup analysis of the AML19 study evaluated outcomes with CPX-351 vs FLAG-Ida in patients with high-risk MDS to provide valuable insights into the potential role of CPX-351 in this patient population.

Methods

The study design and eligibility criteria of AML19 have been previously described⁶. Briefly, patients were randomized 2:1 (in favor of CPX-351) to two induction courses of CPX-351 or FLAG-Ida⁶. AML19 primarily enrolled patients aged <60 years; older patients could enroll if deemed fit by the treating physician⁶. Patients for this subgroup analysis had high-risk MDS ($\geq 10\%$ blasts or 5%–9% blasts with revised IPSS-R score >3.5)⁶.

The primary endpoint was OS defined as time from randomization to death from any cause with those still alive censored at the date last seen and per the revised International Working Group criteria. Other endpoints included RFS, EFS (measured in all patients, and defined as the time from randomization to treatment failure [refractory disease or partial response] by the end of course 2, disease relapse, or death from any cause), CR (based on investigator's assessment of bone marrow), ORR (complete remission or complete remission with incomplete neutrophil or platelet recovery), and toxicity (including time to platelet and neutrophil recovery, and frequency of adverse events [AEs]). CR was defined by the bone marrow regenerating normal hemopoietic cells and containing $<5\%$ blast cells by morphology in an aspirate sample with at least 200 nucleated cells, an absolute neutrophil count $>1000/\mu\text{L}$, and a platelet count $\geq 100/\mu\text{L}$. CR with incomplete recovery was defined as CR except for residual neutropenia ($<1000/\mu\text{L}$) or thrombocytopenia ($<100,000/\mu\text{L}$). Toxicity was scored using the National Cancer Institute Common Toxicity Criteria version 3⁶.

The study was designed to be largely descriptive, without hypothesis testing. Patient characteristics were summarized across the treatment arms using frequency with percentage for categorical data and mean with standard deviation (SD) and median with interquartile range (IQR) for quantitative data. Time-to-event outcomes were compared using log-rank

tests and Cox regression, or Gray's test for cumulative incidence. Proportions were compared using chi-square test. Outcomes are reported as effect sizes with 95% CI. Multiplicity was not adjusted, and p-values presented are nominal and do not imply statistical significance. The final data cutoff was on May 17, 2022 ⁶.

Results

Of the AML19 high-risk cohort, 30% (n = 57) of patients were classified as high-risk MDS (CPX-351, n = 34; FLAG-Ida, n = 23) ⁶. Baseline characteristics were generally well balanced between treatment arms. The proportion of male patients was identical in both groups (65%), and mean age was similar between CPX-351 and FLAG-Ida arms (54.0 vs 53.5 years). Cytogenetic risk categories were comparable, with adverse-risk cytogenetics observed in 65% and 70% of patients, respectively, and TP53 mutations were present in 44% and 48%, respectively. A lower percentage of patients had a World Health Organization performance status of 0–1 in the CPX-351 than the FLAG-Ida arm (88% vs 96%; **Table S1**).

CPX-351 reduced the risk of death by 48% (HR 0.52; 95% CI: 0.27–0.98; p = 0.04), extending the median (95% CI) OS to 17.8 (8.4–not estimable [NE]) months (vs 10.8 [5.7–15.6] months for FLAG-Ida), and increasing the 3-year OS rate to 34% vs 7% with FLAG-Ida (p = 0.04; **Figure 1A**). Notably, in patients with an adverse-risk karyotype (CPX-351, n = 22; FLAG-Ida, n = 16), CPX-351 prolonged the median OS (95% CI) to 13.4 (8–NE) months (vs 12.0 [9.1–15.6] months for FLAG-Ida), showing a trend towards reduced risk of death (HR 0.62; 95% CI: 0.3–1.31; p = 0.21). In patients with baseline bone marrow blasts <10% (CPX-351, n = 11; FLAG-Ida, n = 6), CPX-351 extended the median (95% CI) OS to 19.5 (6.6–NE) months (vs 4.9 [0.1–NE] months for FLAG-Ida), with a trend to reduced risk of death (HR 0.73; CI: 0.41–1.31 p = 0.29). However, in patients with baseline bone marrow blasts 10%–19% (CPX-351, n = 22; FLAG-Ida, n = 14), median OS (95% CI) was similar in both arms (CPX-351, 12.1 [6.0–NE] months; FLAG-Ida, 12.9 [5.6–17.5] months; HR 0.79; CI: 0.52–1.18; p = 0.25).

CPX-351 also lowered the risk of relapse or death by 56% (HR 0.44; 95% CI: 0.2–0.97; p = 0.04). CPX-351 extended median (95% CI) RFS to 19.1 (6.3–NE) months (vs 7 [4.5–9.1] months for FLAG-Ida), with estimated 3-year RFS rates of 43% vs 10%,

respectively (survival probability $p = 0.04$; **Figure 1B**). Median EFS (95% CI) was similar in both arms (CPX-351, 9.4 [6.0–NE] months; FLAG-Ida, 8.9 [3.2–10.4] months; HR 0.59; 95% CI: 0.32–1.11; $p = 0.1$). Estimated 3-year EFS was 35% and 9% for CPX-351 and FLAG-Ida, respectively (survival probability $p = 0.1$). ORR was similar between the CPX-351 and FLAG-Ida arms after both induction course 1 (65% vs 61%) and induction course 2 (76% vs 82%; **Table S2**).

The rate of HCT was 59% and 52% for CPX-351 and FLAG-Ida, respectively ($p = 0.75$). CPX-351 extended the median (95% CI) survival from HCT to 22.3 (5.8–NE) months (vs 11.6 [3.9–20.4] months for FLAG-Ida), with a trend to improved survival (HR 0.44; 95% CI: 0.17–1.14; $p = 0.09$; **Figure 1C**). Median OS (95% CI) was also longer among patients who did not receive an HCT who were treated with CPX-351 vs FLAG-Ida (8.0 [4.4–17.8] vs 5.1 [0.1–9.1] months; HR 0.59; 95% CI: 0.36–0.96; $p = 0.035$; **Figure 1D**).

In the high-risk MDS population, median (IQR) time to platelet recovery in course 1 was similar with CPX-351 vs FLAG-Ida (35 [30, 49] vs 30.5 [29, 35] days; $p = 0.18$), as was neutrophil recovery (37 [28, 44] vs 32.5 [30, 37] days; $p = 0.39$; **Figure S1**). In course 2, median (IQR) platelet recovery trended towards being shorter with CPX-351 vs FLAG-Ida (47 [24, 54] vs 61 [53, 64] days; $p = 0.34$) and median (IQR) neutrophil recovery was shorter (33 [27, 41] vs 49.5 [40, 55] days; $p = 0.0027$).

CPX-351 reduced the cumulative incidence of non-relapse mortality compared with FLAG-Ida ($p = 0.047$; **Figure 2**). However, early mortality rates were not significantly different for CPX-351 vs FLAG-Ida (Day 30: 3% vs 13% [$p = 0.18$]; Day 60: 6% vs 13% [$p = 0.36$]).

Fewer patients in the CPX-351 arm discontinued the study drug than in the FLAG-Ida arm (9% vs 19%). No patients in the CPX-351 arm and two patients (8%) in the FLAG-Ida arm discontinued due to AEs. The rate of serious AEs was lower with CPX-351 versus FLAG-Ida (9% vs 61%; **Table S3**). The most frequently reported serious AEs with FLAG-Ida were hypokalemia (22%), infection (17%), neutropenic sepsis (17%), and sepsis (17%), whereas serious AEs were infrequent with CPX-351 and included hypokalemia and infection (3% each). No patients died due to an AE in the CPX-351 arm; AEs led to death in three patients (13%) in the FLAG-Ida arm.

Discussion

High-risk MDS represents a significant clinical challenge, characterized by poor survival outcomes¹⁴. This exploratory analysis of the AML19 study suggests a potential OS and RFS advantage with CPX-351 vs FLAG-Ida in adult patients with newly diagnosed high-risk MDS. The observed reduction in non-relapse mortality with CPX-351 may have contributed to the longer survival observed in this treatment arm, potentially reflecting differences in treatment-related toxicity or complications during therapy and subsequent transplant pathways. Despite similar response rates between treatment arms, the observed trends toward improved OS and RFS with CPX-351 suggest that factors beyond initial response may contribute to outcomes. The lower incidence of serious AEs suggests that CPX-351 may have a more favorable overall toxicity profile than FLAG-Ida in adult patients with newly diagnosed high-risk MDS. These findings are particularly relevant given the limited randomized data available for treating patients with high-risk MDS¹³. Future studies with larger patient numbers are needed to confirm these findings and clarify the potential benefits of CPX-351 in high-risk MDS. Recent results from the randomized phase 2 PALOMA study (NCT04061239) support the use of CPX-351 as a bridge to HCT in patients with high-risk MDS or oligoblastic AML. After a median follow-up of 38 months, the study demonstrated an improvement in EFS with CPX-351 compared with conventional care regimens (either 7+3 therapy or azacitidine; median: not reached [NR] vs 11.1 months, stratified log-rank test $p=0.0263$). At interim analysis, median OS was not reached for the CPX-351 arm compared with 35.4 months for the CCR arm. No new safety signals were observed.¹⁵ Some limitations must be considered when interpreting the UK NCRI AML19 results. The sample size is small, and this exploratory post hoc analysis was not powered to show generalizable differences in the broader population of patients with high-risk MDS. In addition, the observed post-HCT survival findings should be interpreted with caution, as post-transplant analyses are susceptible to selection (guarantee-time) bias.

In conclusion, these findings suggest that CPX-351 may represent a promising frontline treatment option for high-risk MDS, particularly for patients eligible for HCT. CPX-351 may not only serve as an effective bridge to transplant but also has the potential to improve post-transplant outcomes, warranting further research in a larger population of patients with high-risk MDS.

Data Sharing and Data Availability

All relevant data are provided with the manuscript and supporting files. Jazz has established a process to review requests from qualified external researchers for data from Jazz-sponsored clinical trials in a responsible manner that includes protecting participant privacy, assurance of data security and integrity, and furthering scientific and medical innovation. Additional details on Jazz Pharmaceuticals data sharing criteria and process for requesting access can be found at: <https://www.jazzpharma.com/science/clinical-trial-data-sharing/>.

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Declaration of generative AI use

n/a

Ethics approval statement

The clinical trial was approved by the Wales Multi-centre Research Ethics Committee and each institution's ethics committee in accordance with the Declaration of Helsinki.

ISRCTN registry: ISRCTN78449203

Conflicts of Interest

P Mehta has received speaker/consultancy fees from AbbVie, Astellas Pharma, Daiichi-Sankyo, Jazz Pharmaceuticals, Menarini, Novartis, Otsuka, Pfizer, and Servier.

T Skacel, A Legg, S Faderl, R Murphy, and S Park are employees of and hold stock in Jazz Pharmaceuticals.

A Thomas and S Johnson have no relationships to disclose.

Author Contributions

Priyanka Mehta: Conceptualization; data curation; investigation; project administration; supervision; validation; visualization; writing – review and editing. **Tomas Skacel:** Conceptualization; validation; writing – review and editing. **Stefan Faderl:** Writing – review and editing. **Roderick Murphy:** Writing – review and editing. **Saemi Park:** Data curation; formal analysis; methodology; visualization; writing – review and editing. **Abin Thomas:** Writing – review and editing. **Sean Johnson:** Data curation; validation; writing – review and editing. **Alex Legg:** Visualization; writing – original draft preparation; writing – review and editing.

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Ethics declaration

Informed consent and patient details

Written informed consent to take part in the study and to publish the article has been obtained from all participants or their legal representatives. The privacy rights of participants have been observed.

Studies in Human

This study was performed in compliance with relevant laws, regulatory frameworks and guidelines where the research took place.

This study was approved by the Wales Multicenter Research Ethics Committee .

(Approval No. ISRCTN78449203)

Clinical Trials

The results of this clinical trial and any associated work have been posted in a registry.

This clinical trial was registered with number ISRCTN78449203 ().

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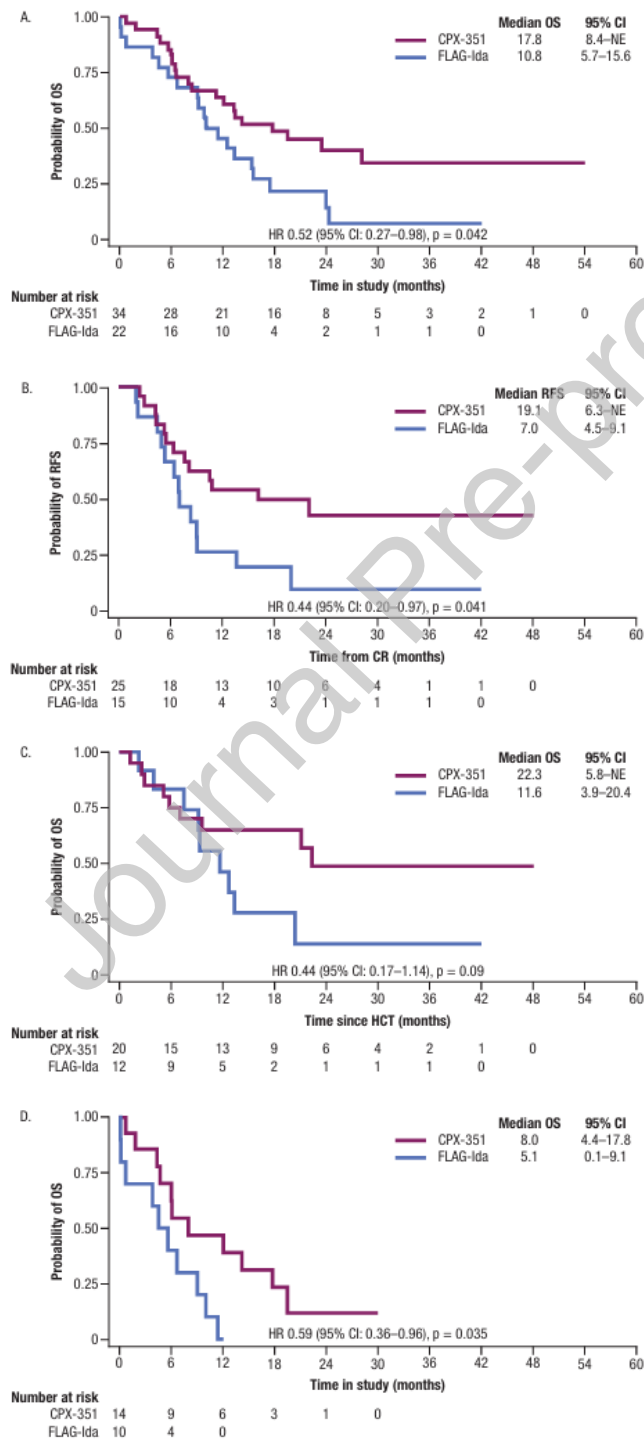
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Figure Legends

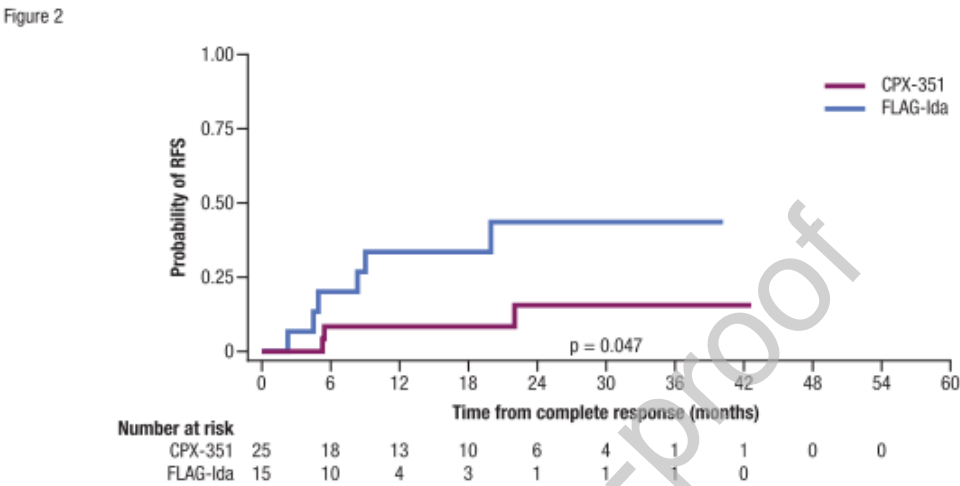
Figure 1. Comparison between CPX-351 and FLAG-Ida (A) OS in the overall high-risk MDS population, (B) RFS in patients who achieved CR, (C) OS landmarked at HCT, (D) OS patients who did not receive HCT

Figure 1



Abbreviations: CI, confidence interval; CR, complete response; FLAG-Ida, fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin; HCT, hematopoietic cell transplant; HR, hazard ratio; MDS, myelodysplastic syndrome; NE, not estimable; OS, overall survival; RFS, relapse-free survival.

Figure 2. Cumulative incidence of death in patients who achieved CR



Abbreviations: CR, complete response; FLAG-Ida, fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin; RFS, relapse-free survival.