P592 A Randomized Comparison of CPX-351 and FLAG-Ida in High-Risk Myelodysplastic Syndrome (MDS): a Subgroup Analysis of UK NCRI AML19

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Background

- CPX-351, a dual-drug liposomal encapsulation of daunorubicin and cytarabine in a synergistic 1:5 molar ratio, is approved for newly diagnosed, therapy-related acute myeloid leukemia (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[1-3]
- These approvals were based on the primary analysis of the pivotal phase 3 trial (ClinicalTrials.gov Identifier: NCT01696084), in which CPX-351 demonstrated significantly improved median overall survival (OS: 9.56 vs 5.95 months; hazard ratio [HR]: 0.69; 95% confidence interval [CI]: 0.52, 0.90; one-sided *P*=0.003) and remission rates (complete remission [CR] + CR with incomplete neutrophil or platelet recovery [CRi]; 47.7% vs 33.3%; two-sided *P*=0.016) vs conventional 7+3 chemotherapy after a median follow-up of 20.7 months and a comparable safety profile in older adults aged 60-75 years with newly diagnosed high-risk or secondary AML[4]
  - After 5 years of follow-up, improved median overall survival with CPX-351 was maintained (HR: 0.70; 95% CI: 0.55, 0.91]), and consistent with the prior primary analysis[5]
- Another randomized, controlled, open-label, phase 3 study, UK NCRI AML19 trial (ISRCTN78449203), compared efficacy and safety of CPX-351 vs 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]
  - There was no difference in OS or event-free survival (EFS) between treatment arms, but median relapse-free survival (RFS) in patients achieving CR was longer with CPX-351 (22.1 vs 8.35 months; HR: 0.66; 95% CI: 0.41, 1.06; *P*=0.08)

Objective

- This exploratory subgroup analysis of the AML19 study evaluated outcomes with CPX-351 vs FLAG-Ida in the high-risk MDS subgroup

Methods

- Study design and eligibility criteria of AML19 have been previously described[6]
- Patients were randomized 2:1 to CPX-351 or FLAG-Ida
  - CPX-351 induction dose was 100 units/m^2 (cytarabine 100 mg/m^2 and daunorubicin 44 mg/m^2) on days 1, 3, and 5 for cycle 1, and 100 units/m^2 on days 1 and 3 in cycle 2; consolidation was up to 2 cycles of 65 units/m^2 CPX-351 (cytarabine 65 mg/m^2 and daunorubicin 29 mg/m^2) on days 1 and 3
  - FLAG-Ida consisted of fludarabine 30 mg/m^2 and cytarabine 2 g/m^2 on days 2-6 (reduced to 1 g/m^2 in patients >60 years), lenograstim 263 µg on days 1-7, and idarubicin 8 mg/m^2 on days 4-6; consolidation regimens were amsacrine, cytarabine, and etoposide (MACE), then mitoxantrone and cytarabine (MiDAC)
- AML19 primarily enrolled patients aged <60 years; older patients could enroll if deemed fit by the treating physician
- Patients for this subgroup analysis had high-risk MDS (defined as ⩾10% blasts or 5%-9% blasts with revised international prognostic scoring system [IPSS-R] score >3.5)
- 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)
- Other endpoints included OS in patients who received hematopoietic cell transplant (HCT; landmarked at date of HCT), RFS, EFS, overall response rates (ORR; defined as CR+CRi), and toxicity (including time to platelet [to >100 x10^9/L] and neutrophil [to >1 x10^9/L] recovery, and frequency of adverse events [AE])
- Time-to-event outcomes were compared using log-rank tests and Cox regression (without covariates)
  - Outcomes were reported as effect sizes with 95% CIs
  - All comparison *P* values were nominal

Results

Table 1. Baseline Characteristics of Patients With High-Risk MDS by Treatment Arm

	CPX-351 (n=34)	FLAG-Ida (n=23)
Male, n (%)	22 (65)	15 (65)
Age, mean (SD), years	54.0 (9.6)	53.5 (9.4)
Age group (years), n (%)		
<30	1 (3)	0
30-39	3 (9)	3 (13)
40-49	6 (18)	4 (17)
50-59	15 (44)	8 (35)
⩾60	9 (26)	8 (35)
WBC (x10^9/L), n (%)		
<10	30 (88)	22 (96)
10 to <50	1 (3)	0
50 to <100	3 (9)	1 (4)
WHO PS, n (%)		
0 (normal activity)	11 (32)	14 (61)
1 (strenuous activity restricted, but ambulatory)	19 (56)	8 (35)
2 (<50% of daytime in bed)	4 (12)	1 (4)
Cytogenetic group, n (%)[a]		
Normal	4 (12)	2 (9)
Intermediate	5 (15)	3 (13)
Adverse	23 (68)	16 (70)
No results[b]	2 (6)	2 (9)

[a]Patients who would classify as intermediate or adverse cytogenetic grouping based on either 1998 or 2009 criteria were included in the adverse cytogenetic group.

[b]Refers to missing or not conducted.

FLAG-Ida, fludarabine, cytarabine, granulocyte-colony stimulating factor, and idarubicin; MDS, myelodysplastic syndrome; SD, standard deviation; WBC, white blood cell, WHO PS, World Health Organization performance status.

- Of the entire AML19 high-risk cohort, 30% (n=57) were classified as high-risk MDS, of whom 34 and 23 were randomized to CPX-351 and FLAG-Ida, respectively[6]
- Baseline characteristics were generally similar between the CPX-351 and FLAG-Ida arms, except a higher percentage of patients in the CPX-351 arm had a WHO PS of 1-2 vs the FLAG-Ida arm

Table 2. Response Rates by Treatment Cycle

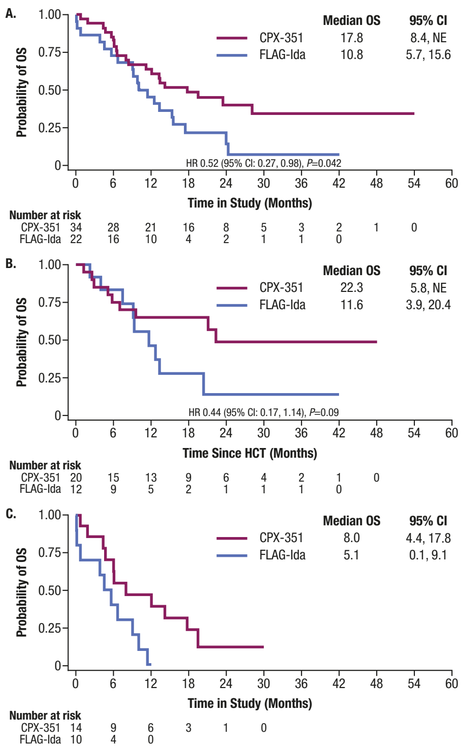
Response	CPX-351 (n=34)	FLAG-Ida (n=23)
After cycle 1	n=34	n=23
ORR	22 (65)	14 (61)
CR	17 (50)	10 (43)
CRi	5 (15)	4 (17)
After cycle 2	n=34	n=22
ORR	26 (76)	18 (82)
CR	25 (74)	15 (68)
CRi	1 (3)	3 (14)

Data are n (%).

CR, complete response; CRi, CR with incomplete neutrophil or platelet recovery; FLAG-Ida, fludarabine, cytarabine, granulocyte-colony stimulating factor, and idarubicin; ORR, overall response rate.

- ORR was similar between treatment arms after both induction cycle 1 (CPX-351, 65%; FLAG-Ida, 61%) and 2 (CPX-351, 76%; FLAG-Ida, 82%)

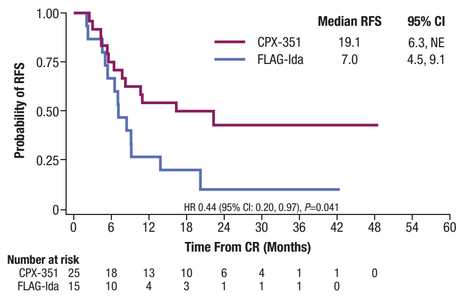
Figure 1. Comparison of OS Between CPX-351 and FLAG-Ida (A) in the Overall High-Risk MDS Population, (B) Landmarked at HCT, (C) in Patients Who Did Not Receive HCT



CI, confidence interval; 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.

- Kaplan-Meier–estimated 3-year OS was higher with CPX-351 vs FLAG-Ida (34% vs 13%, respectively; *P*=0.04) and the median OS was 17.8 vs 10.8 months, respectively
  - In patients with an adverse-risk karyotype (CPX-351, n=23; FLAG-Ida, n=16), median OS (95% CI) was higher with CPX-351 vs FLAG-Ida (13.4 [8, not estimable (NE)] vs 12.0 [9.1, 15.6] months, respectively)
  - In patients with baseline bone marrow blasts <10% (CPX-351, n=11; FLAG-Ida, n=6), median OS (95% CI) was 19.5 (6.6, NE) with CPX-351 and 4.9 (0.1, 24.0) with FLAG-Ida
  - For patients with baseline bone marrow blasts 10%-19% (CPX-351, n=22; FLAG-Ida, n=14), median OS was similar in both arms (CPX-351, 12.1 [6.0, NE] months; FLAG-Ida, 12.9 [5.6, 17.5] months)
- The rate of HCT was numerically higher with CPX-351 vs FLAG-Ida, respectively (at any time, 59% vs 52%, *P*=0.75; in first response [defined as CR or CRi], 65% vs 56%, *P*=0.51)
- Median OS from HCT date was longer among patients treated with CPX-351 vs FLAG-Ida (22.3 vs 11.6 months)
- Median OS was also longer among patients who did not receive an HCT who were treated with CPX-351 vs FLAG-Ida (8.0 vs 5.1 months)

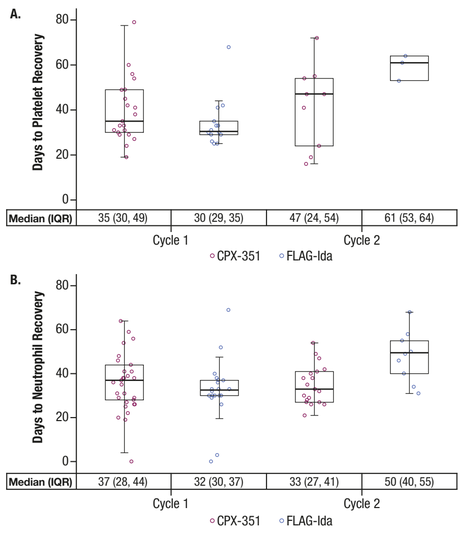
Figure 2. Comparison of RFS Between CPX-351 and FLAG-Ida



CI, confidence interval; FLAG-Ida, fludarabine, cytarabine, granulocyte-colony stimulating factor, and idarubicin; HR, hazard ratio; NE, not estimable; RFS, relapse-free survival.

- The CPX-351 arm demonstrated superior estimated 3-year RFS vs FLAG-Ida (43% vs 10%, respectively; *P*=0.04)
- Estimated 3-year EFS was 35% and 14% for CPX-351 and FLAG-Ida, respectively (*P*=0.1)

Figure 3. Days to (A) Platelet and (B) Neutrophil Recovery[a] by Randomization and Treatment Cycle



Data are median (IQR). Each circle represents a patient who achieved hematologic recovery. The horizontal line within each box represents the median. The box borders represent the IQR. Upper and lower error bars represent Q3+(1.5*IQR) and Q1-(1.5*IQR), respectively, to indicate maximum and minimum points before individual points are considered outliers.

[a]Days to recovery were defined as the difference from the date that chemotherapy started to the date of recovery.

FLAG-Ida, fludarabine, cytarabine, granulocyte-colony stimulating factor, and idarubicin; IQR, interquartile range; Q, quartile.

- In the high-risk MDS population, median time to platelet recovery in cycle 1 was similar with CPX-351 vs FLAG-Ida (*P*=0.18), as was neutrophil recovery (*P*=0.39)
- However, in cycle 2, while platelet recovery was similar (*P*=0.34), neutrophil recovery was significantly shorter (*P*=0.0027) with CPX-351 vs FLAG-Ida

Table 3. Summary of AEs by Treatment Arm

	CPX-351 (n=34)	FLAG-Ida (n=23)
AE (any grade)	33 (97)	23 (100)
AE (grade ⩾3)	26 (76)	16 (70)
AEs leading to discontinuation	0	2 (8)
SAE	3 (9)	14 (61)
Most common SAEs[a]		
Anorexia	0	3 (13)
Hypokalemia	1 (3)	5 (22)
Infection[b]	1 (3)	4 (17)
Neutropenia throughout	0	3 (13)
Neutropenic sepsis	0	4 (17)
Persistent neutropenia	0	2 (9)
Prolonged thrombocytopenia	0	2 (9)
Sepsis	0	4 (17)

Data are n (%).

[a]Occurring in ⩾5% of patients in each treatment arm. Any individual patient could have experienced ⩾1 AE.

[b]Infection includes encephalitis, polymicrobial sepsis, urinary infection, Hickman line infections, pneumonia, neutropenic septicemia, or anal abscess.

AE, adverse event; FLAG-Ida, fludarabine, cytarabine, granulocyte-colony stimulating factor, and idarubicin; SAE, serious adverse event.

- Day 30 and 60 mortality rates were 3% and 6% for CPX-351 and 13% and 13% for FLAG-Ida (day 30, *P*=0.18; day 60, *P*=0.36), respectively
- Overall, 3 patients (9%) in the CPX-351 arm and 5 (19%) in the FLAG-Ida arm discontinued the study drug
  - No patients in the CPX-351 arm and 2 patients (8%) in the FLAG-Ida arm discontinued due to AEs
- The rate of serious AEs was considerably lower with CPX-351 vs FLAG-Ida; specifically, the incidence of infection, sepsis, and myelosuppression was lower in patients treated with CPX-351
- AEs led to death in 3 patients (13%) in the FLAG-Ida arm, whereas no patient died due to an AE in the CPX-351 arm

Conclusions

- This AML19 exploratory analysis suggests a survival advantage, including improved RFS and post-HCT OS, with CPX-351 compared with FLAG-Ida in adult patients with newly diagnosed high-risk MDS
- The lower incidence of serious AEs (infection, sepsis, and myelosuppression) suggests that CPX-351 may have a more favorable overall toxicity profile than FLAG-Ida in adult patients with newly diagnosed high-risk MDS
- Limitations include the small sample size and the exploratory nature of this post-hoc analysis of the AML19 study
- Future studies with larger patient numbers are needed to confirm these findings

References: 1. VYXEOS® (daunorubicin and cytarabine) Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals Inc; 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209401s011lbl.pdf. Last accessed April 2024. **2.** European Medicines Agency (EMA). Vyxeos liposomal summary of product characteristics. 2022. Available at: https://www.ema.europa.eu/en/documents/product-information/vyxeos-liposomal-epar-product-information_en.pdf. Last accessed April 2024. **3.** Electronic Medicines Compendium. Vyxeos liposomal summary of product characteristics. 2023. Available at: https://www.medicines.org.uk/emc/product/9442/smpc#gref. Last accessed April 2024. **4.** Lancet JE, et al. *J Clin Oncol.* 2018;36(26):2684-2692. **5.** Lancet JE, et al. *Lancet Haematol.* 2021;8(7):e481-e491. **6.** Othman J, et al. *Blood Adv.* 2023;7(16):4539-4549.

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