# PF492 Evolution of Real-World Treatment Pathways for Secondary Acute Myeloid Leukemia in England

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## Background

- Secondary acute myeloid leukemia (sAML) is a high-risk disease with a poor prognosis[1]
- Over the past 5-10 years, the treatment landscape for sAML in England has evolved significantly
- In late 2018, the National Institute for Health and Care Excellence (NICE) recommended CPX-351, a dual-drug liposomal encapsulation of daunorubicin and cytarabine in a synergistic 1:5 molar ratio, for newly diagnosed, therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC)[2,3]
- CPX-351 was approved for newly diagnosed t-AML or AML-MRC in adults in the EU/UK[4,5] based on results from a pivotal phase 3 trial in older adults with newly diagnosed high-risk/sAML (ClinicalTrials.gov Identifier: NCT01696084)[2,6]
  - After a median follow-up of 5 years, CPX-351 improved overall survival (OS) vs conventional 7+3 chemotherapy; Kaplan-Meier (KM) estimates of 3-year and 5-year OS were 21% vs 9% and 18% vs 8%, respectively[6]
  - The safety profile of CPX-351 was similar to that of conventional 7+3 therapy[2]
- At the onset of the coronavirus disease 2019 (COVID-19) pandemic in 2020, venetoclax was made available through an emergency measure as an alternative to intensive treatment to protect high-risk patients and save resources[7,8]
- In February 2022, NICE recommended venetoclax + azacitidine for treatment-naïve adults with AML ineligible for intensive treatment[9]

## Objective

- To examine the evolution of front-line (1L) treatment patterns for sAML in England over time, including hematopoietic cell transplant (HCT) rates and post-HCT survival

## Methods

- This retrospective population cohort study included adults with sAML (t-AML, AML with prior myelodysplastic syndrome, or chronic myelomonocytic leukemia) who received 1L systemic treatment in England between January 1, 2013, and April 30, 2024
- Patient records were sourced from England's Cancer Analysis System (CAS) database, available through the National Cancer Registration and Analysis Service
  - Electronic medical records from the Cancer Outcomes and Services Dataset (COSD) and COSD-linked Hospital Episode Statistics (HES) inpatient secondary care were used to identify patient diagnoses
  - HES inpatient and outpatient care data were used to identify HCT
- OS was estimated from the diagnosis and landmarked from the HCT date
  - Survival probabilities were estimated using the KM method

## Results

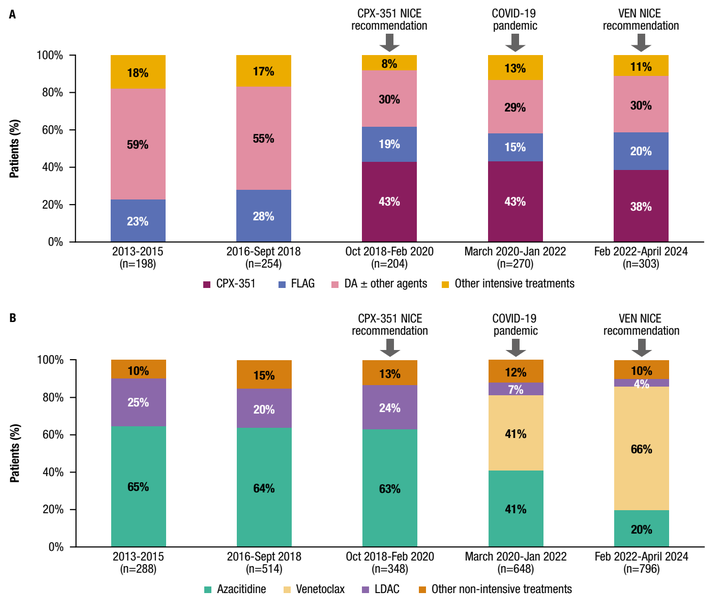
**Table 1. Patients Characteristics According to 1L Treatment for sAML**

| | All Patients (N=4464) | CPX-351 (n=321) | DA ± Other Agent (n=487) | FLAG (n=255) | Venetoclax (n=789) | Azacitidine (n=1159) | LDAC (n=335) | Other Treatments[a] (n=478) | Trial (n=640) |
|---|---|---|---|---|---|---|---|---|---|
| **Age at diagnosis, years** | | | | | | | | | |
| Mean (SD) | 68 (12) | 62 (9) | 60 (12) | 55 (13) | 72 (8) | 73 (9) | 75 (7) | 74 (10) | 64 (12) |
| Median (IQR) | 70 (63, 76) | 63 (57, 68) | 62 (55, 68) | 57 (48, 64) | 73 (68, 77) | 74 (69, 79) | 76 (71, 80) | 76 (70, 81) | 66 (59, 72) |
| **Age categories at diagnosis (years), n (%)** | | | | | | | | | |
| 18-59 | 829 (19) | 105 (33) | 207 (43) | 152 (60) | 53 (7) | 83 (7) | 11 (3) | 40 (8) | 178 (28) |
| ≥60 | 3635 (81) | 216 (67) | 280 (57) | 103 (40) | 736 (93) | 1076 (93) | 324 (97) | 438 (92) | 462 (72) |
| **Sex, n (%)** | | | | | | | | | |
| Female | 1732 (39) | 121 (38) | 217 (45) | 104 (41) | 295 (37) | 393 (34) | 138 (41) | 190 (40) | 274 (43) |
| Male | 2732 (61) | 200 (62) | 270 (55) | 151 (59) | 494 (63) | 766 (66) | 197 (59) | 288 (60) | 366 (57) |
| **Ethnicity, n (%)** | | | | | | | | | |
| White | 4032 (90) | 281 (88) | 438 (90) | 220 (86) | 708 (90) | 1066 (92) | 315 (94) | 430 (90) | 574 (90) |
| Asian | 214 (5) | 19 (6) | 27 (6) | 17 (7) | 37 (5) | 48 (4) | 13 (4) | 21 (4) | 32 (5) |
| Other[b] | 218 (5) | 21 (7) | 22 (5) | 18 (7) | 44 (6) | 45 (4) | 7 (2) | 27 (6) | 34 (5) |
| **AML subtype, n (%)** | | | | | | | | | |
| t-AML | 2082 (47) | 165 (51) | 242 (50) | 154 (60) | 383 (49) | 499 (43) | 145 (43) | 208 (44) | 286 (45) |
| AML with a prior MDS or CMML diagnosis | 2382 (53) | 156 (49) | 245 (50) | 101 (40) | 406 (51) | 660 (57) | 190 (57) | 270 (56) | 354 (55) |

[a]Other treatments group contains a mixture of intensive chemotherapies (high-dose cytarabine, mitoxantrone, etoposide-based) and less intensive treatments (enasidenib, ivosidenib, and vosoroxin-based); [b]Other ethnicity groups were Mixed, Black, and Chinese/Other.
1L, front-line; AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; DA, daunorubicin/cytarabine; FLAG, fludarabine, high-dose cytarabine, and granulocyte colony-stimulating factor; IQR, interquartile range; LDAC, low-dose cytarabine; MDS, myelodysplastic syndrome; sAML, secondary acute myeloid leukemia; SD, standard deviation; t-AML, therapy-related acute myeloid leukemia.

- In total, 4464 patients were included within the study; of those, 1229 received intensive treatment, 2595 received non-intensive treatment, and 640 were treated in a clinical trial setting
- There was a general trend of younger age in patients undergoing intensive treatment compared to non-intensive treatment
- Of the 1229 patients receiving intensive treatment, more patients treated with CPX-351 were aged over 60 years (67%) than patients receiving daunorubicin/cytarabine (DA; 57%) or fludarabine, high-dose cytarabine, and granulocyte colony-stimulating factor (FLAG)-based regimens (40%)

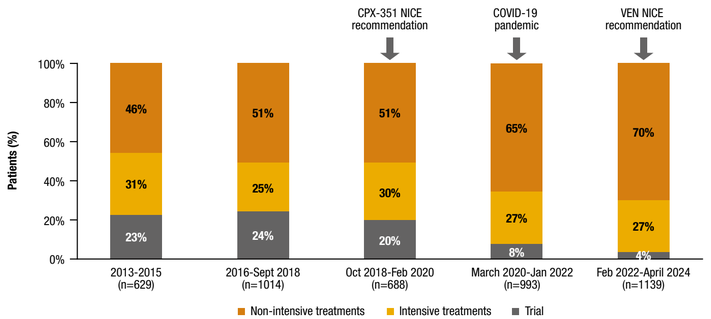
**Figure 1. Changes Over Time in (A) Intensive Treatment and (B) Non-Intensive Treatment for 1L sAML Treatment in England**




1L, front-line; COVID-19, coronavirus disease 2019; DA, daunorubicin/cytarabine; FLAG, fludarabine, high-dose cytarabine, and granulocyte colony-stimulating factor; LDAC, low-dose cytarabine; NICE, National Institute for Health and Care Excellence; sAML, secondary acute myeloid leukemia; VEN, venetoclax.

- Prior to CPX-351's NICE recommendation, 1L intensive treatment was primarily DA regimens followed by FLAG-based regimens
- Following the recommendation, CPX-351 rapidly became the standard-of-care intensive treatment and remained so pre- and post–COVID-19
- Non-intensive treatment choices changed during COVID-19 with rapid adoption of venetoclax-based therapy, which continued to grow after its NICE recommendation, mainly displacing low-dose cytarabine (LDAC) and azacitidine monotherapy

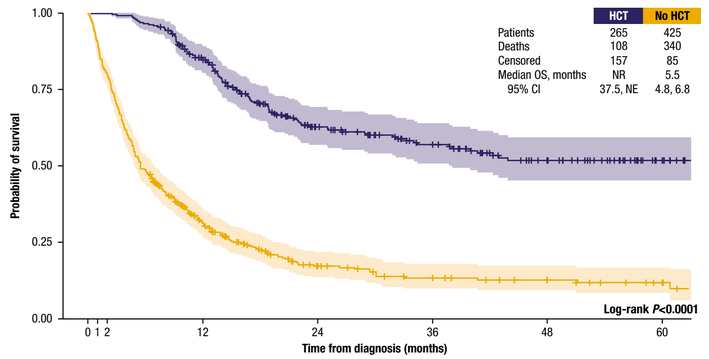
**Figure 2. Dynamics of 1L Treatment of sAML Over Time**




1L, front-line; COVID-19, coronavirus disease 2019; NICE, National Institute for Health and Care Excellence; sAML, secondary acute myeloid leukemia; VEN, venetoclax.

- Over time, intensive treatment use remained largely constant at 25-31%
- Clinical trial participation reduced over time from 24% (2016-Sept 2018) to 4% (Feb 2022-June 2024), likely driven by the closure of the National Cancer Research Institute AML working group studies
- Since the COVID-19 pandemic, non-intensive treatments for sAML became more prevalent, from 51% (2016-Sept 2018) to 70% (Feb 2022-April 2024) of patients with sAML, driven by increased treatment with venetoclax

**Figure 3. Kaplan-Meier–Estimated OS From Diagnosis in Patients With sAML Who Received Intensive 1L Treatment (by HCT Status)**

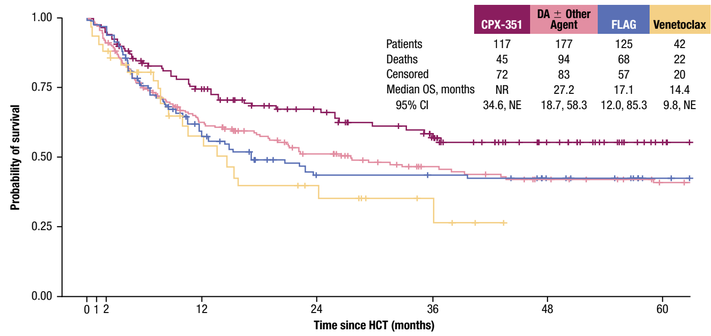



| Time Since Diagnosis | HCT n at Risk | HCT Probability of Survival (95% CI) | No HCT n at Risk | No HCT Probability of Survival (95% CI) |
|---|---|---|---|---|
| 1 month | 265 | 1.00 (1.00, 1.00) | 377 | 0.88 (0.85, 0.92) |
| 2 months | 265 | 1.00 (1.00, 1.00) | 340 | 0.80 (0.76, 0.83) |
| 1 year | 212 | 0.85 (0.80, 0.89) | 108 | 0.31 (0.27, 0.36) |
| 2 years | 121 | 0.63 (0.57, 0.69) | 41 | 0.17 (0.14, 0.22) |
| 3 years | 87 | 0.57 (0.51, 0.64) | 24 | 0.13 (0.10, 0.18) |

Only includes patients who received 1L treatment after Oct 2018. Shading indicates the 95% CI.
1L, front-line; CI, confidence interval; HCT, hematopoietic cell transplant; NE, not estimable; NR, not reached; OS, overall survival; sAML, secondary acute myeloid leukemia.

- In an unadjusted analysis, HCT improved survival in sAML; estimated 3-year OS was higher with HCT (57%; 95% confidence interval [CI]: 51, 64) vs without (13%; 95% CI: 10, 18; log-rank $P<0.0001$)
- A small degree of immortal time bias may have been introduced in this analysis because patients had a delay in HCT after diagnosis

**Figure 4. Kaplan-Meier–Estimated OS Landmarked From HCT in Patients With sAML (by 1L Treatment)**

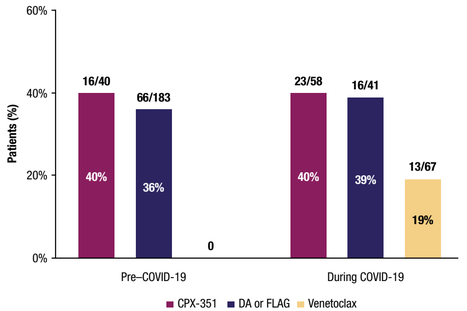



| Time From HCT | CPX-351 n at Risk | CPX-351 Probability of Survival (95% CI) | DA ± Other n at Risk | DA ± Other Probability of Survival (95% CI) | FLAG n at Risk | FLAG Probability of Survival (95% CI) | Venetoclax n at Risk | Venetoclax Probability of Survival (95% CI) |
|---|---|---|---|---|---|---|---|---|
| 1 year | 80 | 0.74 (0.67, 0.83) | 103 | 0.62 (0.56, 0.70) | 65 | 0.58 (0.50, 0.68) | 16 | 0.58 (0.43, 0.77) |
| 2 years | 57 | 0.67 (0.59, 0.77) | 72 | 0.51 (0.44, 0.59) | 39 | 0.44 (0.35, 0.54) | 9 | 0.40 (0.25, 0.62) |
| 3 years | 40 | 0.58 (0.49, 0.69) | 52 | 0.46 (0.39, 0.55) | 38 | 0.44 (0.35, 0.54) | * | 0.35 (0.21, 0.58) |

*<6 patients (in compliance with the NCRAS small number suppression guidelines, as outlined by National Health Service Digital, patient counts <6 are not presented to remove any possibility of patient re-identification).
1L, front-line; CI, confidence interval; DA, daunorubicin/cytarabine; FLAG, fludarabine, high-dose cytarabine, and granulocyte colony-stimulating factor; HCT, hematopoietic cell transplant; OS, overall survival; NCRAS, National Cancer Registration and Analysis Service; NE, not estimable; NR, not reached; sAML, secondary acute myeloid leukemia.

- In patients with sAML treated with 1L intensive treatment, estimated 3-year OS post-HCT was numerically superior for CPX-351 (58%; 95% CI: 49, 69) vs DA regimens (46%; 95% CI: 39, 55) or FLAG (44%; 95% CI: 35, 54)
- Patients with sAML bridged to HCT with venetoclax had inferior OS post-HCT (estimated 3-year OS: 35% [95% CI: 21, 58]) compared to all intensive treatment regimens

**Figure 5. HCT Rates by 1L Treatment Received and Treatment Period**




Pre–COVID-19 included data from 2013 to March 2020. During COVID-19 included data from March 2020 to January 2022. Venetoclax patients treated before March 1, 2020 (n=8) are transferred to the during COVID-19 period.
1L, front-line; COVID-19, coronavirus disease 2019; DA, daunorubicin/cytarabine; FLAG, fludarabine, high-dose cytarabine, and granulocyte colony-stimulating factor; HCT, hematopoietic cell transplant.

- HCT rates following intensive treatment were similar pre–COVID-19 and during COVID-19
- Following emergency approval of venetoclax during COVID-19, the HCT rate for venetoclax-treated patients was 19% (13/67 patients)

## Conclusions

- In patients with sAML, CPX-351 was rapidly adopted post-NICE recommendation and remains the standard-of-care intensive treatment
- Venetoclax use began during COVID-19, growing further after NICE's 2022 recommendation and replacing LDAC and azacitidine monotherapy
- HCT remains key for optimal outcomes, with CPX-351 improving post-HCT survival vs DA regimens or FLAG, even though CPX-351-treated patients were, on average, older; venetoclax-treated patients had the poorest post-HCT survival
- This study is limited by its observational nature, the lack of propensity score methods, and the lack of key molecular or cytogenetics data in the CAS database, which may limit risk stratification and confound outcome interpretation, particularly given the biological heterogeneity within sAML populations
- These findings, utilizing the large CAS database patient population from across England, highlight the impact of COVID-19 and national reimbursement recommendations on 1L sAML treatment, and highlight the importance of continuing to evaluate real-world effectiveness and safety

**References: 1.** Winer ES. *Hematol Oncol Clin North Am.* 2020;34:449-463. **2.** Lancet JE, et al. *J Clin Oncol.* 2018;36(26):2684-2693. **3.** National Institute for Health and Care Excellence. Liposomal cytarabine–daunorubicin for untreated acute myeloid leukaemia. 2018. Available at: https://www.nice.org.uk/guidance/ta552/chapter/2-Information-about-liposomal-cytarabinedaunorubicin. Accessed April 15, 2025. **4.** Vyxeos liposomal (44 mg/100 mg powder for concentrate for solution for infusion) summary of product characteristics. European Medicines Agency: Jazz Pharmaceuticals Ireland, Ltd.; 2024. **5.** Electronic Medicines Compendium. Vyxeos liposomal 44 mg/100 mg powder for concentrate for solution for infusion. 2025. Available at: https://www.medicines.org.uk/emc/product/9442/smpc#gref. Accessed April 15, 2025. **6.** Lancet JE, et al. *Lancet Haematol.* 2021;8(7):e481-e491. **7.** Othman J, et al. *Blood Neoplasia.* 2024;1(3):100017. **8.** Othman J, et al. *Blood.* 2021;138 (Supplement 1):2321. **9.** National Institute for Health and Care Excellence. Venetoclax with azacitidine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable. 2022. Available at: https://www.nice.org.uk/guidance/TA765/chapter/1-Recommendations. Accessed April 15, 2025.

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This work uses data that have been provided by patients and collected by NHS England, as part of their care and support of cancer patients. The data are collated, maintained, and quality assured by the National Disease Registration Service, which is part of NHS England. Access to this data was facilitated by the Simulacrum produced by Health Data Insight CIC. Simulacrum is a synthetic dataset based on the real data. It is made available for development of programming and analysis code which is then used on the real data in the CAS to produce the analyses in this study. Simulacrum was developed with financial support from IQVIA.

**Disclosures: A Lambova**, **E Ralphs**, **K Keapoletswe**, and **G Wester** are employees of IQVIA Inc., which was contracted by Jazz Pharmaceuticals for the conduct of this analysis. **A Legg** is an employee of and holds stock in Jazz Pharmaceuticals.



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