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# POSTER ABSTRACTS

## 613.ACUTE MYELOID LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

### What Is the Optimal Treatment Modality in Molecularly Defined Secondary AML? a Multicenter Cohort Study

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*Introduction*

Secondary ontogeny acute myeloid leukemia (AML), defined by the presence of mutations in *ASXL1*, *BCOR*, *EZH2*, *SF2B1*, *SRSF2*, *STAG2*, *U2AF1* or *ZRSR2* was recently integrated into both the ICC and WHO diagnostic criteria, as well as into the ELN 2022 risk classification as adverse risk. However, it is unknown whether cytarabine + anthracycline (7+3), liposomal cytarabine and daunorubicin (CPX-351) or hypomethylating agent + venetoclax (HMA+VEN) is the optimal frontline treatment for these patients (pts). We performed the largest multicenter retrospective cohort study to date, dedicated to pts with molecular-defined secondary ontogeny AML, comparing treatment modalities and assessing the impact of clinical and molecular characteristics on response and survival.

*Methods*

We included pts with newly diagnosed (ND) AML who were treated at 4 large academical centers with 7+3, CPX-351 or HMA+VEN. Secondary ontogeny was defined as absence of *TP53* mutation and presence of at least one of the aforementioned mutations. Composite complete response (cCR) was defined as complete response (CR) + CR with incomplete count recovery (CRi). Logistic regression was fitted to evaluate odds ratio (OR) for cCR. Overall survival (OS) was compared between groups by log-rank test. COX regression for OS were fitted to evaluate effect of secondary/co-mutations within each treatment group, as well as the effect of treatment and allogeneic stem cell transplantation (SCT) as a time-varying covariate.

*Results*

Out of 1132 ND AML pts in the entire cohort, 401 (35%) were molecularly defined as secondary ontogeny and included in the final analysis. Initial treatment was 7+3 in 173 (43%), HMA+VEN in 162 (40%) and CPX-351 in 66 pts (17%). Pts in the HMA+VEN group were older (median age 74 years[yrs]; CPX351 66 yrs; 7+3 63 yrs, $p<0.001$), while pts in the CPX351 group were more likely to have prior myeloid neoplasm (n=52 [79%]; HMA+VEN n=72 [44%]; 7+3 n=48 [28%], $p<0.001$) and prior HMA exposure (n=27 [41%]; HMA+VEN n=23 [14%]; 7+3 n=28 [16%], $p<0.001$).

The cCR rates were 56% (97/173), 56% (90/162) and 44% (29/66) in 7+3, HMA+VEN and CPX-351, respectively ($p=0.21$). In the 7+3 group, the presence of *RUNX1* co-mutation was associated with lower cCR rate (OR 0.8, 95% confidence interval [CI]

0.7-0.95, p=0.01), while *PTPN11* was associated with higher cCR rate (OR 1.4, 95% CI 1.1-1.8, p=0.011). In the HMA+VEN group, monosomal karyotype (OR 0.7, 95% CI 0.5-0.9, p=0.002), *NRAS* co-mutation (OR 0.6, 95% CI 0.5-0.8, p<.001) and *SF3B1* mutation (OR 0.76, 95% CI 0.6-0.9, p=0.008) were associated with lower cCR rate and *FLT3-TKD* with higher cCR rate (OR 1.5, 95% CI 1.1-2.1, p=0.01). In the CPX-351 group, *NRAS* co-mutation was associated with lower cCR rate (OR 0.65, 95% CI 0.5-0.9, p=0.005).

As most younger pts (aged ≤ 60 yrs, n=85) were treated with 7+3 (n=64) or CPX-351 (n=13) and almost exclusively older pts (age >75, n=78) were treated with HMA+VEN (n=74), we performed age-group based analyses. In pts aged > 60 yrs (n=318), the median OS (mOS) was comparable between groups (7+3: 16 months [mo], 95% CI 13-27; HMA+VEN 15 mo, 95% CI 13-19; CPX-351 11 mo, 95% CI 9-28 p=0.57). Similar results were seen in pts 60-75 yrs (n=238): 7+3 mOS 16 mo, 95% CI 13-27; HMA+VEN mOS 16 mo, 95% CI 13-26; CPX-351 mOS 10 mo, 95% CI 8-28, p=0.74.

The effect of secondary/co-mutations on survival differ between groups: For 7+3 splicing mutations were associated with worse OS, whereas *IDH1/2* were associated with improved OS ( **Figure**). Conversely, in HMA+VEN and CPX351 groups *K/NRAS* co-mutations were associated with worse survival. *NPM1* co-mutation did not affect survival in any treatment group. In multivariable analysis, age, prior myeloid disease, *K/NRAS* co-mutations and monosomal karyotype were associated with worse OS ( **Table**). Conversely, *BCOR* mutation, *IDH1/2* co-mutation and SCT were associated with improved OS. Treatment with HMA+VEN or CPX351 were not statistically different *vs* 7+3, although there was a trend for better OS with HMA+VEN *vs* 7+3 (HR 0.68, 95% CI 0.44-1.03, p=0.069).

*Conclusion*

In pts with ND secondary ontogeny AML the OS with HMA+VEN was at least comparable to 7+3 or CPX351 when adjusted for multiple covariates. The effect of co-mutations on response and OS differed between treatment modalities and may aid in optimal treatment selection in this population. Prospective trials should evaluate the potential superiority of HMA+VEN and effect of co-mutations in secondary ontogeny AML.

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| Covariate | Univariable analysis (HR, CI 95%) | p-value | Multivariable analysis (HR, CI 95%) | p-value |
|---|---|---|---|---|
| **Age** | 1.03 (1.01, 1.04) | <0.001 | **1.04 (1.02, 1.06)** | **<0.001** |
| Sex (male vs. female) | 1.04 (0.79, 1.38) | 0.77 | | |
| **Prior myeloid disease** | 1.78 (1.37, 2.32) | <0.001 | **1.90 (1.38, 2.62)** | **<0.001** |
| Prior HMA exposure | 1.42 (1.04, 1.92) | 0.025 | | |
| Karyotype | | | | |
| - normal | 0.77 (0.58, 1.02) | 0.064 | | |
| - **Monosomal** | 1.97 (1.34, 2.89) | <0.001 | **1.86 (1.24, 2.79)** | **0.003** |
| - Complex | 1.62 (1.11, 2.36) | 0.013 | | |
| Molecular | | | | |
| - *SRSF2* | 0.82 (0.61, 1.11) | 0.20 | | |
| - *SF3B1* | 1.50 (1.09, 2.07) | 0.013 | | |
| - *U2AF1* | 1.23 (0.87, 1.75) | 0.25 | | |
| - *ZRSR2* | 0.44 (0.11, 1.79) | 0.25 | | |
| - *ASXL1* | 1.14 (0.87, 1.48) | 0.34 | | |
| - ***BCOR*** | 0.61 (0.41, 0.90) | 0.012 | **0.60 (0.40, 0.92)** | **0.018** |
| - *EZH2* | 1.53 (1.00, 2.33) | 0.050 | 1.54 (0.97, 2.43) | 0.065 |
| - *STAG2* | 1.03 (0.71, 1.50) | 0.88 | | |
| - *FLT3-ITD* | 1.11 (0.72, 1.71) | 0.63 | | |
| - *NPM1* | 1.05 (0.68, 1.63) | 0.81 | | |
| - ***IDH (1/2)*** | 0.59 (0.42, 0.83) | 0.002 | **0.67 (0.46, 0.97)** | **0.035** |
| - ***NRAS/KRAS*** | 1.63 (1.21, 2.20) | 0.001 | **1.81 (1.29, 2.54)** | **<0.001** |
| Treatment (*vs.* 7+3 as baseline) | | | | |
| - HMA+Ven | 1.53 (1.14, 2.05) | 0.004 | 0.68 (0.44, 1.03) | 0.069 |
| - CPX351 | 1.48 (1.02, 2.15) | 0.041 | 0.85 (0.54, 1.34) | 0.48 |
| **AlloSCT as time-varying covariate** | 0.37 (0.27, 0.51) | <0.001 | **0.37 (0.25, 0.54)** | **<0.001** |

**Table. COX regression univariable and multivariable analysis for OS.** All variables with p<.1 in the univariate model and pre-defined variables of treatment and alloSCT as time varying covariate were included in the multivariable model. **In bold**: covariates with a p<.05 in the multivariable model. HR – hazard ratio; HMA – hypomethylating agents; Ven – venetoclax; AlloSCT – allogeneic stem cell transplantation.

| | Sec. mutations (HR, 95% CI) | *Co-mutations* (HR, 95% CI) | | |
|---|---|---|---|---|
| | Splicing *vs.* non-splicing | *IDH (IDH1/2)* | *RAS (NRAS/KRAS)* | *NPM1* |
| 7+3 | 1.64 (1.02-2.64) p=0.042 | 0.48 (0.29-0.81) p=0.006 | 1.4 (0.88-2.21) p=0.18 | 0.85 (0.41-1.77) p=0.67 |
| HMA+Ven | 0.69 (0.44-1.07) p=0.094 | 0.9 (0.54-1.49) p=0.67 | 2.3 (1.35-3.93) p=0.002 | 1.21 (0.67-2.18) p=0.53 |
| CPX351 | 1.07 (0.57-2.01) p=0.84 | 0.49 (0.18-1.39) p=0.18 | 2.12 (1.12-4.00) p=0.021 | 1.52 (0.36-6.33) p=0.57 |

**Figure. Effect of secondary mutations type and co-mutations on overall survival within each treatment group.** Presented with Hazard ratio (HR), 95% confidence interval (CI) and p values. Secondary splicing mutations: *SRSF2, SF3B1, U2AF1, ZRSR2*; secondary non-splicing mutations: *ASXL1, BCOR, STAG2, EZH2*.

**Figure 1**

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