AML-095

Findings From an Analysis of Patients With Monocytic and Monocytic-Like Acute Myeloid Leukemia (AML), Including AML-M4 and AML-M5, Treated With Venetoclax (Ven) Plus Azacitidine (Aza)

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OBJECTIVE

To report findings by acute myeloid leukemia differentiation state using the French-American-British classification system (M4, M5) and gene expression profiling to define monocytic acute myeloid leukemia from a post hoc analysis of venetoclax + azacitidine in patients ineligible for intensive chemotherapy (pooled analyses of M14-358 and VIALE-A)

CONCLUSIONS

Remission rates and survival outcomes were not differentiated between patients with French-American-British–defined or gene expression profiling–defined monocytic state in this dataset

Differences in response and survival among patients with monocytic AML were most closely linked to the presence or absence of prognostically relevant mutations such as *NPM1* and *N/KRAS*

Although the baseline expression of BCL-2 family members associated with differentiation state was similar across these select mutational groups, the differences in combination with the downstream effects of these mutations appear to influence the outcomes to Ven+Aza

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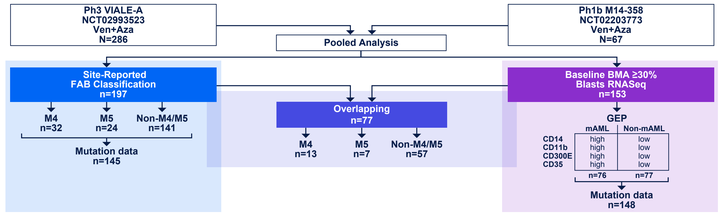
BACKGROUND

- Venetoclax (Ven) + azacitidine (Aza) has shown broad efficacy across different subgroups of patients with acute myeloid leukemia (AML) who are ineligible for intensive chemotherapy
- In monocytic AML (mAML), ex vivo studies have shown that Ven may have reduced activity[1-3]; possible reasons include decreased *BCL2* expression and increased *MCL1* and *BCL2A1* expression
  - Overrepresentation of activating mutations in signaling genes (eg, *FLT3-ITD, KRAS, NRAS, PTPN11*)
- However, outcomes reported in clinical studies have been mixed
  - A study of 100 patients suggested that those with an M5 AML may be less sensitive to Ven+Aza[4]
  - Another study of 54 patients suggested monocytic differentiation was not predictive for patient outcomes[3]

METHODS

- Patients from the M14-358 and VIALE-A studies who received Ven+Aza were included (**Figure 1**)
- 2 methods were used to define mAML
  - Pathologic assignment of French-American-British (FAB) subtyping per investigator
  - Baseline gene expression profiling (GEP)
- For GEP, expression levels of genes associated with monocytic differentiation (*CD14*, *ITGAM [CD11b]*, *CD300e*, *and CR1 [CD35]*) were used to classify patients as mAML (high) or non-mAML (low); scan QR code for **Supplemental Materials** and see Figure S1
- Complete remission (CR) + CR with incomplete count recovery (CRi) rates and median overall survival were assessed
- RNA sequencing and mutational profiling using MyAML targeted panel were performed on baseline bone marrow aspiration specimens
- Gene expression of BCL-2 family members were determined for individual mutation subgroups

Figure 1. Consort Diagram

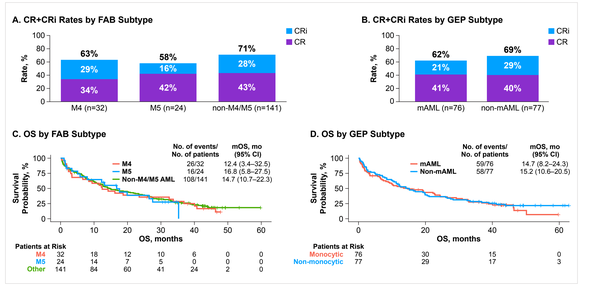


Aza, azacitidine; BMA, bone marrow aspiration; FAB, French-American-British; GEP, gene expression profiling; mAML, monocytic acute myeloid leukemia; Ph, phase; RNAseq, RNA sequencing; Ven, venetoclax.

RESULTS

- Clinical outcomes were similar between FAB subtypes and GEP subtypes (**Figure 2**)
- CR+CRi rates with Ven+Aza treatment were similar between patients with mAML with *NPM1*, *IDH1/2*, or *FLT3-ITD* mutations but were substantially lower among patients with mAML and *N/KRAS* mutation (33%; **Table 1**)
- Mutation prevalence by FAB subtype and overlapping mutations are in the **Supplemental Materials** (Tables S1 and S2)
- Molecular characteristics and/or molecular drivers in combination with differentiation state are more predictive of survival outcomes than differentiation state alone (**Figure 3**). Overall survival for *IDH1*, *IDH2*, and *TP53* are in the **Supplemental Materials** (Figure S2)
- BCL-2 family expression across mAML vs non-mAML is in the **Supplemental Materials** (Figure S3), along with *MCL1* gene expression by mutation type in mAML vs non-mAML (Figure S4)
- Among patients with mAML, expression of *BCL2* was lower and *BCL2A1* was higher compared to non-mAML across all mutation types; expression of *BCL2L1* in *N/KRAS* was higher in mAML vs non-mAML, which differed from other mutation types (**Figure 4**)

Figure 2. Clinical Outcomes by Subtype



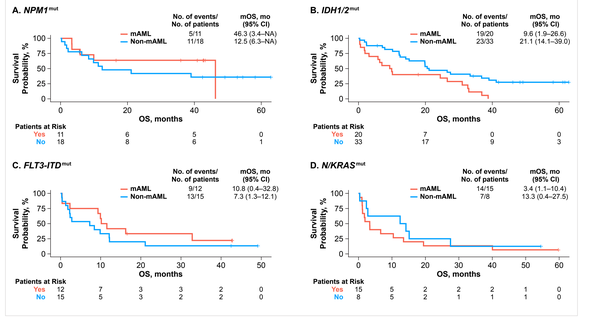
CR, complete remission; CRi, complete remission with incomplete count recovery; FAB, French-American-British; GEP, gene expression profiling; mAML, monocytic acute myeloid leukemia; mOS, median overall survival; OS, overall survival.

Table 1. CR+CRi for Patients Treated With Ven+Aza by Mutations in the GEP-Defined Subtypes

	mAML, n=74		Non-mAML, n=74	
	n (%)	CR+CRi, % (95% CI)	n (%)	CR+CRi, % (95% CI)
Mutation				
NPM1	11 (14.9)	63.6 (35.4–84.8)	18 (24.3)	72.2 (49.1–87.5)
IDH1/2	20 (27.0)	55.0 (34.2–74.2)	33 (44.6)	81.8 (65.6–91.4)
FLT3-ITD	12 (16.2)	58.3 (32.0–80.7)	15 (20.3)	53.3 (30.1–75.2)
N/KRAS	15 (20.3)	33.3 (15.2–58.3)	8 (10.8)	75.0 (40.9–92.8)
TP53	10 (13.5)	50.0 (23.7–76.3)	11 (14.9)	54.5 (28.0–78.7)

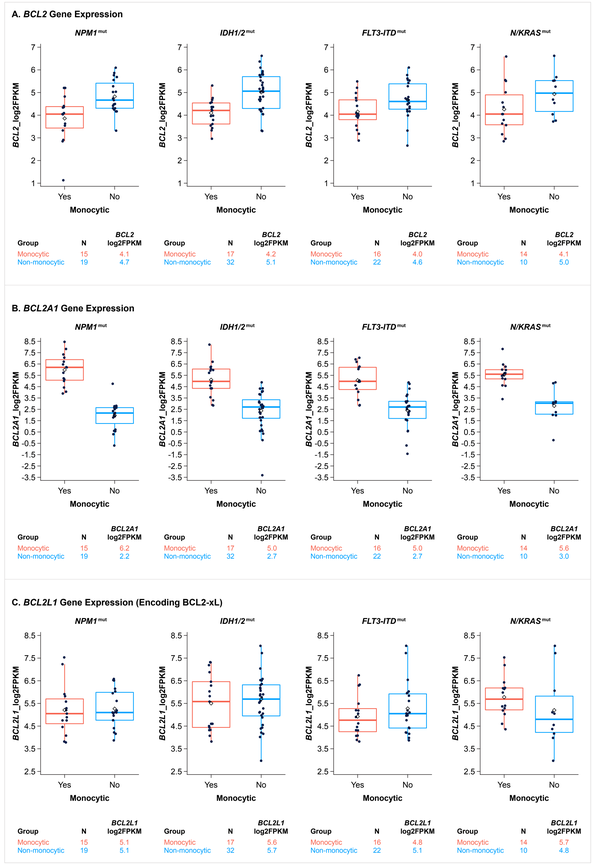
Aza, azacitidine; CR, complete remission; CRi, complete remission with incomplete count recovery; GEP, gene expression profiling; mAML, monocytic acute myeloid leukemia; mut, mutation; Ven, venetoclax.

Figure 3. OS for Patients Treated With Ven+Aza by Mutation and mAML vs Non-mAML Status



Aza, azacitidine; mAML, monocytic acute myeloid leukemia; mOS, median overall survival; mut, mutation; NA, not applicable; OS, overall survival; Ven, venetoclax.

Figure 4. Gene Expression by Mutation Type in mAML vs non-AML



mAML, monocytic acute myeloid leukemia; mut, mutation.