(PF526) ZEFAMENIB COMBINED WITH CHEMOTHERAPY OR TARGETED AGENTS IN PATIENTS WITH ACUTE MYELOID LEUKEMIA: PRELIMINARY RESULT OF AN OPEN-LABEL, PHASE I/II STUDY

Topic: 04. Acute myeloid leukemia - Clinical

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Background

Zefamenib is a potent small molecule inhibitor targeting menin, which has demonstrated anti-leukemia efficacy and safety in relapsed/refractory (R/R) acute leukemia patients in a phase 1 study. However, the safety and efficacy of zefamenib combined with intensive chemotherapy or venetoclax and azacitidine in AML remains unknown.

Aims

To evaluate the safety and efficacy of zefamenib combined with intensive chemotherapy or venetoclax and azacitidine (VA regimen) in AML.

Methods

This is an open-label, multicenter, phase I/II study (NCT06746519). Eligible patients should be AML, aged 18 years or older, harboring *KMT2A/NUP98* rearrangement or *NPM1* mutation with intermediate or adverse risk. This study comprised the following 3 groups. Group A enrolled untreated AML patients who were fit for intensive chemotherapy. Group B enrolled untreated AML patients unfit for intensive chemotherapy. Group C enrolled R/R AML patients who showed resistance to zefamenib monotherapy. Patients in group A received induction with zefamenib and 7+3, followed by high-dose cytarabine consolidation for a maximum of 4 cycles. Patients in group B and C received induction and cosolidation therapy with zefamenib, venetoclax and azacitidine. Allo-HSCT can be implemented after CR. In all 3 groups, zefamenib was planned to be given at a 3+3 dose escalation of 200mg; 400mg or 600mg BID since day 4 of cycle 1 and day 1 of the following cycles. Primary endpoints were safety and recommended phase 2 dose. Secondary endpoints included composite CR rate, CR rate, duration of remission and overall survival.

Results

Since Nov, 2024, a total of 27 patients were screened. Twenty-six patients were enrolled and one screened failure. The median age of the patients were 40.5 (range: 30-58) years old and 12 patients (46.2%) were male. Of whom, 24 (92.3%) were primary AML and 2 (7.7%) were secondary AML. Twenty patients (76.9%) were newly diagnosed AML, 2 (7.7%) were relapsed AML and 4 (15.4%) were refractory AML. Four (15.4%) had previously menin inhibitor exposure history. Patient baseline characteristics was shown in Table 1.Twenty-five (96.2%) patients were evaluable for treatment response. Of whom, 21 patients (80.8%) achieved CRc, all were CR. Four patients (15.4%) should no response. The CRc rates in untreated AML and R/R AML patients were 90% (18/20) and 50% (3/6), respectively, and all were CR. The CRc and CR rate in patients received zeftamenib plus chemotherapy and zeftamenib plus venetoclax and azacitidine (VA) were both 87.5% (17/18) and 77.8% (14/18), respectively (Table 2). 12/25 patients (46.2%, 95% CI: 26.59-66.63) achieved measurable residual disease (MRD) negative remission. Of the 21 patients with *KMT2A* rearrangement, 16 (76.2%) achieved CR, and MRD negative remission was observed in 9 patients (42.9%, 95% CI: 21.82-65.99) (Table 3). The 9-months rate of duration of remission was 72% (95% CI: 23.79-92.76). At the date of data cutoff (Dec 20, 2025), only one patient (3.8%) was dead. The 12-months overall survival rate was 96% (95% CI: 74.84-99.43) (Figure 1, 2). Grade 3 or higher infections were observed in 7 patients (26.9 %), including 37.5% and 22.2% of patients treated with zeftamenib plus chemotherapy and VA, respectively. Sepsis were observed in one patient (12.5%) treated with zeftamenib and chemotherapy.

Summary/Conclusion

Zefamenib-based combination therapies demonstrated a high response rate in treatment-naïve AML patients, and also exhibited notable efficacy in patients with zefamenib resistance.

Table 1: Baseline characteristics of patients

	Group A-200mg (N=6) n(%)	Group A-400mg (N=2) n(%)	Combined with Chemotherapy (N=8) n(%)	Group B-200mg (N=8) n(%)	Group B-400mg (N=4) n(%)	Group C-200mg (N=5) n(%)	Group C-400mg (N=1) n(%)	Combined with VA (N=18) n(%)	Total (N=26) n(%)
Disease Subtype									
Primary AML	6 (100.0)	2 (100.0)	8 (100.0)	8 (100.0)	4 (100.0)	4 (80.0)	0 (0.0)	16 (88.9)	24 (92.3)
Secondary AML	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	1 (100.0)	2 (11.1)	2 (7.7)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
FAB Classification									
AML-M0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AML-M1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AML-M2	2 (33.3)	0 (0.0)	2 (25.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	3 (11.5)
AML-M3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AML-M4	0 (0.0)	1 (50.0)	1 (12.5)	1 (12.5)	1 (25.0)	1 (20.0)	1 (100.0)	4 (22.2)	5 (19.2)
AML-M5	3 (50.0)	0 (0.0)	3 (37.5)	5 (62.5)	2 (50.0)	2 (40.0)	0 (0.0)	9 (50.0)	12 (46.2)
AML-M6	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AML-M7	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	1 (16.7)	1 (50.0)	2 (25.0)	1 (12.5)	1 (25.0)	2 (40.0)	0 (0.0)	4 (22.2)	6 (23.1)
Disease Status									
Newly Diagnosed Disease	6 (100.0)	2 (100.0)	8 (100.0)	8 (100.0)	4 (100.0)	0 (0.0)	0 (0.0)	12 (66.7)	20 (76.9)
Relapsed Disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	1 (100.0)	2 (11.1)	2 (7.7)
Refractory Disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (80.0)	0 (0.0)	4 (22.2)	4 (15.4)
Has previously Menin inhibitor therapy been received									
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (60.0)	1 (100.0)	4 (22.2)	4 (15.4)
No	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (40.0)	0 (0.0)	2 (11.1)	2 (7.7)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Percentages are calculated with the number of patients in each group of the mITT population as the denominator.
FAB: The French-American-British. ELN: European LeukemiaNet.

Table 2: Results of overall efficacy evaluation

Efficacy Indicators	Group A-200mg (N=6) n(%)	Group A-400mg (N=2) n(%)	Combined with Chemotherapy (N=8) n(%)	Group B-200mg (N=8) n(%)	Group B-400mg (N=4) n(%)	Group C-200mg (N=5) n(%)	Group C-400mg (N=1) n(%)	Combined with VA (N=18) n(%)	Total (N=26) n(%)
Best Overall Response									
CR	6 (100.0)	1 (50.0)	7 (87.5)	8 (100.0)	3 (75.0)	3 (60.0)	0 (0.0)	14 (77.8)	21 (80.8)
CRh	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CRi	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
MLFS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No Response	0 (0.0)	1 (50.0)	1 (12.5)	0 (0.0)	1 (25.0)	1 (20.0)	1 (100.0)	3 (16.7)	4 (15.4)
Haematologic Relapse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not Evaluable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (5.6)	1 (3.8)
ORR									
n (%)	6 (100.0)	1 (50.0)	7 (87.5)	8 (100.0)	3 (75.0)	3 (60.0)	0 (0.0)	14 (77.8)	21 (80.8)
95% CI	54.07, 100.00	1.26, 98.74	47.35, 99.68	63.06, 100.00	19.41, 99.37	14.66, 94.73	0.00, 97.50	52.36, 93.59	60.65, 93.45
CR and CR with Partial Hematologic Recovery									
n (%)	6 (100.0)	1 (50.0)	7 (87.5)	8 (100.0)	3 (75.0)	3 (60.0)	0 (0.0)	14 (77.8)	21 (80.8)
95% CI	54.07, 100.00	1.26, 98.74	47.35, 99.68	63.06, 100.00	19.41, 99.37	14.66, 94.73	0.00, 97.50	52.36, 93.59	60.65, 93.45
Composite Complete Remission (CRc)									
n (%)	6 (100.0)	1 (50.0)	7 (87.5)	8 (100.0)	3 (75.0)	3 (60.0)	0 (0.0)	14 (77.8)	21 (80.8)
95% CI	54.07, 100.00	1.26, 98.74	47.35, 99.68	63.06, 100.00	19.41, 99.37	14.66, 94.73	0.00, 97.50	52.36, 93.59	60.65, 93.45

Note: Objective Response Rate (ORR), Defined as investigator-assessed complete remission (CR), complete remission with partial hematologic recovery (CRh), complete remission with incomplete hematologic recovery (CRi), morphologic leukemia-free state (MLFS), or partial remission (PR). The formula is as follows: ORR=n1/N, n1=CR+PR+CRh+CRi+MLFS.

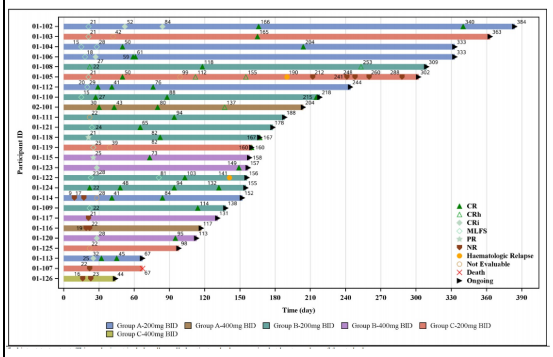

Figure 1: Swimming plot of the patients

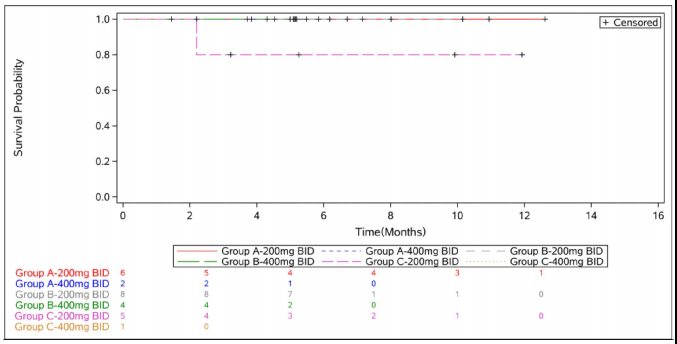

Figure 2: Overall survival curve