ZIFTOMENIB COMBINED WITH VENETOCLAX/AZACITIDINE IN RELAPSED/REFRACTORY *NPM1*-M OR *KMT2A*-R ACUTE MYELOID LEUKEMIA: INTERIM PHASE 1A RESULTS FROM KOMET-007

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INTRODUCTION

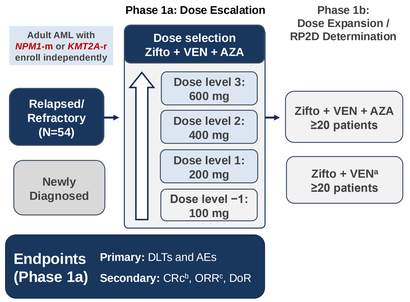
- In approximately 35–40% of acute myeloid leukemia (AML) cases, leukemogenesis is driven either by *NPM1* mutations or by *KMT2A* rearrangements[1,2]
- KMT2A (MLL) and NPM1 sit upstream from major AML targets, including FLT3 and IDH1/2[3]
- Ziftomenib – a potent, selective oral menin inhibitor – has shown clinical activity as monotherapy in adult relapsed/refractory (R/R) *NPM1*-mutated (*NPM1*-m) or *KMT2A*-rearranged (*KMT2A*-r) AML[4]
- Patients with R/R AML have a poor prognosis, with a less than 20% expected response rate following venetoclax + azacitidine[5–8]
- KOMET-007 is an ongoing, open-label, dose escalation (phase 1a) and expansion (phase 1b) study to evaluate ziftomenib in combination with standard chemotherapies in adults with newly diagnosed and R/R *NPM1*-m or *KMT2A*-r AML (NCT05735184)

METHODS

Study Design and Patients

- KOMET-007 study design is shown in **Figure 1**
- Ziftomenib dosing started on Cycle 1 Day 8 and was administered continuously thereafter
- Venetoclax (VEN) was administered per label in 28-day cycles; adjustments to cycle length based on Cycle 1 bone marrow biopsy results
- Azacitidine was administered per label on Cycle 1 Days 1–7; additional cycles based on bone marrow biopsy results

Figure 1. Study Design of KOMET-007



[a]*Zifto + VEN only for NPM1-m patients;* [b]*CR, CRh, or CRi;* [c]*CRc or MLFS.*

AE, adverse event; AML, acute myeloid leukemia; AZA, azacitidine; CRc, composite complete remission; CRh, complete remission with partial hematological recovery; CRi, complete remission with incomplete hematological recovery; DLT, dose-limiting toxicity; DoR, duration of response; MLFS, morphologic leukemia-free state; ORR, objective response rate; RP2D, recommended phase 2 dose; VEN, venetoclax; Zifto, ziftomenib.

RESULTS

Patients

- Baseline patient characteristics are shown in **Table 1**
- As of the October 1, 2024 data cutoff, 54 patients were enrolled into separate and independent dose-escalation cohorts

Table 1. Baseline Patient Characteristics in R/R AML

	All Patients N=54[a]	*NPM1*-m				*KMT2A*-r			
		200 mg n=7	400 mg n=7	600 mg n=12	Total n=26	200 mg n=11	400 mg n=9	600 mg n=7	Total n=28[a]
Median age, years (range)	59 (22–86)	55 (41–77)	71 (45–86)	68 (34–76)	69 (34–86)	53 (23–71)	45 (32–69)	65 (22–72)	53 (22–72)
Female, n (%)	30 (56)	4 (57)	3 (43)	8 (67)	15 (58)	6 (55)	4 (44)	4 (57)	15 (54)
Race, n (%)									
White	27 (50)	5 (71)	5 (71)	4 (33)	14 (54)	5 (45)	4 (44)	4 (57)	13 (46)
Black/African American	10 (19)	0	0	3 (25)	3 (12)	2 (18)	4 (44)	0	7 (25)
Other/Not Recorded	17 (31)	2 (29)	2 (29)	5 (42)	9 (35)	4 (36)	1 (11)	3 (43)	8 (29)
ECOG PS, n (%)									
1	30 (56)	5 (71)	4 (57)	5 (42)	14 (54)	7 (64)	5 (56)	4 (57)	16 (57)
2	11 (20)	1 (14)	0	4 (33)	5 (19)	2 (18)	1 (11)	2 (29)	6 (21)
Co-mutations, n (%)	31 (57)	5 (71)	5 (71)	9 (75)	19 (73)	6 (55)	3 (33)	3 (43)	12 (43)
FLT3	13 (24)	2 (29)	2 (29)	7 (58)	11 (42)	1 (9)	0	1 (14)	2 (7)
IDH1/2	8 (15)	3 (43)	2 (29)	3 (25)	8 (31)	0	0	0	0
Both *FLT3* and *IDH1/2*	4 (7)	1 (14)	1 (14)	2 (17)	4 (15)	0	0	0	0
Median prior therapies, n (range)	2 (1–8)	2 (1–8)	1 (1–3)	2 (1–4)	2 (1–8)	1 (1–7)	3 (1–6)	2 (1–4)	2 (1–7)
Prior therapy, n (%)									
HSCT	16 (30)	4 (57)	0	2 (17)	6 (23)	3 (27)	5 (56)	1 (14)	10 (36)
Venetoclax	37 (69)	5 (71)	5 (71)	6 (50)	16 (62)	8 (73)	7 (78)	5 (71)	21 (75)
Menin Inhibitors	11 (20)	2 (29)	1 (14)	0	3 (12)	4 (36)	2 (22)	2 (29)	8 (29)

[a]*Includes one patient who did not receive a dose of ziftomenib.*
AML, acute myeloid leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, hematopoietic stem cell transplant.

Safety and Tolerability

- Treatment-emergent adverse events (TEAEs) occurring in ≥20% of all patients are shown in **Table 2**
- Four cases (8%) of differentiation syndrome (DS) occurred in patients receiving ziftomenib; all were manageable, and no discontinuations occurred due to DS: 1 Gr3 *NPM1*-m 400 mg; 1 Gr3 *KMT2A*-r 200 mg; 1 Gr3 *KMT2A*-r 400 mg; 1 Gr2 *KMT2A*-r 400 mg
- No ziftomenib-associated corrected QT interval (QTc) prolongation or dose-limiting toxicities (DLTs) occurred

Table 2. Treatment-Emergent Adverse Events Occurring in ≥20% of All Patients in R/R AML

TEAEs, n (%)	All Patients N=54[a]	*NPM1*-m				*KMT2A*-r			
		200 mg n=7	400 mg n=7	600 mg n=12	Total n=26	200 mg n=11	400 mg n=9	600 mg n=7	Total n=28[a]
Any Grade	53 (98)	6 (86)	7 (100)	12 (100)	25 (96)	11 (100)	9 (100)	7 (100)	28 (100)
Nausea	21 (39)	5 (71)	1 (14)	4 (33)	10 (38)	2 (18)	5 (56)	4 (57)	11 (39)
Constipation	18 (33)	3 (43)	2 (29)	3 (25)	8 (31)	4 (36)	4 (44)	2 (29)	10 (36)
Platelet count decreased	18 (33)	3 (43)	1 (14)	0	4 (15)	6 (55)	5 (56)	3 (43)	14 (50)
Diarrhea	17 (31)	3 (43)	2 (29)	2 (17)	7 (27)	4 (36)	4 (44)	2 (29)	10 (36)
Anemia	16 (30)	1 (14)	2 (29)	0	3 (12)	4 (36)	6 (67)	3 (43)	13 (46)
Febrile neutropenia	15 (28)	1 (14)	2 (29)	2 (17)	5 (19)	3 (27)	5 (56)	2 (29)	10 (36)
Vomiting	15 (28)	2 (29)	1 (14)	2 (17)	5 (19)	3 (27)	4 (44)	3 (43)	10 (36)
Fatigue	13 (24)	3 (43)	2 (29)	4 (33)	9 (35)	0	3 (33)	1 (14)	4 (14)
Decreased appetite	12 (22)	2 (29)	1 (14)	0	3 (12)	4 (36)	4 (44)	1 (14)	9 (32)
Hypokalemia	12 (22)	3 (43)	2 (29)	1 (8)	6 (23)	2 (18)	2 (22)	2 (29)	6 (21)
Hypophosphatemia	12 (22)	2 (29)	2 (29)	1 (8)	5 (19)	5 (45)	2 (22)	0	7 (25)
Hyperphosphatemia	11 (20)	2 (29)	1 (14)	1 (8)	4 (15)	3 (27)	2 (22)	2 (29)	7 (25)
Neutrophil count decreased	11 (20)	1 (14)	1 (14)	0	2 (8)	4 (36)	3 (33)	2 (29)	9 (32)
Grade ≥3	49 (91)	6 (86)	7 (100)	9 (75)	22 (85)	11 (100)	9 (100)	6 (86)	27 (96)
Platelet count decreased	17 (31)	2 (29)	1 (14)	0	3 (12)	6 (55)	5 (56)	3 (43)	14 (50)
Anemia	14 (26)	1 (14)	1 (14)	0	2 (8)	4 (36)	5 (56)	3 (43)	12 (43)
Febrile neutropenia	14 (26)	1 (14)	2 (29)	2 (17)	5 (19)	3 (27)	5 (56)	1 (14)	9 (32)

[a]*Includes 1 patient who did not receive a dose of ziftomenib.*
AML, acute myeloid leukemia; TEAE, treatment-emergent adverse event.

Clinical Activity

- Clinical activity in all response-evaluable R/R patients is shown in **Table 3**

Table 3. Clinical Activity in Response-Evaluable[a] R/R Patients (N=49)

Response, n (%)	*NPM1*-m				*KMT2A*-r			
	200 mg n=7	400 mg n=6	600 mg n=9	Total n=22	200 mg n=11	400 mg n=9	600 mg n=6	Total n=27[b]
CRc	4 (57)	3 (50)	4 (44)	11 (50)	2 (18)	1 (11)	1 (17)	4 (15)
ORR	5 (71)	4 (67)	6 (67)	15 (68)	4 (36)	4 (44)	1 (17)	9 (33)
CR	1 (14)	2 (33)	2 (22)	5 (23)	2 (18)	0	1 (17)	3 (11)
CRh	2 (29)	1 (17)	0	3 (14)	0	1 (11)	0	1 (4)
CRi	1 (14)	0	2 (22)	3 (14)	0	0	0	0
MLFS	1 (14)	1 (17)	2 (22)	4 (18)	2 (18)	3 (33)	0	5 (19)
PR	0	0	0	0	0	0	0	0
NR	2 (29)	2 (33)	1 (11)	5 (23)	6 (54)	5 (56)	4 (67)	15 (56)
NE	0	0	2 (22)	2 (9)	1 (9)	0	1 (17)	3 (11)

[a]*Defined as patients who have ≥1 response assessment or who had died;* [b]*includes 1 patient who did not receive a dose of ziftomenib.*
Per ELN 2022: CR, complete remission; CRc, composite complete remission; CRh, complete remission with partial hematological recovery; CRi, complete remission with incomplete hematological recovery; MLFS, morphologic leukemia-free state; NE, not evaluable; NR, no response; ORR; objective response rate; PR, partial remission.

- Among 11 menin inhibitor-experienced patients (3 *NPM1*-m, *8 KMT2A*-r), there were two responders (200 mg and 400 mg *KMT2A*-r); clinical activity is shown in menin inhibitor-naive patients in **Table 4** and by prior VEN exposure in **Table 5**

Table 4. Clinical Activity in Menin Inhibitor-Naive R/R Patients (N=39)

Response, n (%)	Menin Inhibitor-Naive	
	NPM1-m n=19	*KMT2A*-r n=20
CRc	11 (58)	4 (20)
ORR	15 (79)	7 (35)
CR	5 (26)	3 (15)
CRh	3 (16)	1 (5)
CRi	3 (16)	0
MLFS	4 (21)	3 (15)
PR	0	0
NR	2 (11)	10 (50)
NE	2 (10)	3 (15)

Table 5. Clinical Activity By Prior Venetoclax (N=49)

Response, n (%)	NO Prior VEN		Prior VEN	
	NPM1-m n=8	*KMT2A*-r n=7	*NPM1*-m n=14	*KMT2A*-r n=20
CRc	6 (75)	1 (14)	5 (36)	3 (15)
ORR	**8 (100)**	**3 (43)**	**7 (50)**	**6 (30)**
CR	4 (50)	1 (14)	1 (7)	2 (10)
CRh	1 (13)	0	2 (14)	1 (5)
CRi	1 (13)	0	2 (14)	0
MLFS	2 (25)	2 (29)	2 (14)	3 (15)
PR	0	0	0	0
NR	0	4 (57)	5 (36)	11 (55)
NE	0	0	2 (14)	3 (15)

Per ELN 2022: CR, complete remission; CRc, composite complete remission; CRh, complete remission with partial hematological recovery; CRi, complete remission with incomplete hematological recovery; MLFS, morphologic leukemia-free state; NE, not evaluable; NR, no response; ORR, objective response rate; PR, partial remission; VEN, venetoclax.

- For *NPM1*-m and overall populations, median duration of composite complete remission (CRc) was 23.4 weeks (95% confidence interval [CI] 8.7– not estimable [NE])
- Six *NPM1*-m patients received a stem cell transplant (200 mg n=3, 400 mg n=1, 600 mg n=2); thus far, 1 went onto ziftomenib maintenance (**Figure 2**)
  - 6-Month landmark overall survival (OS) rate was 77% (95% CI 53–90)
- For *KMT2A-r*, median duration of CRc was not reached (95% CI 21.9–NE)
- Three *KMT2A*-r patients received a stem cell transplant (200 mg n=2, 400 mg n=1); thus far, 1 went onto ziftomenib maintenance (**Figure 3**)
  - 6-Month landmark OS rate was 43% (95% CI 23–61)

Figure 2. Duration of Treatment in the *NPM1*-m Cohort

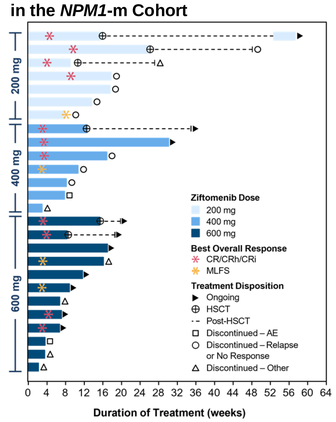
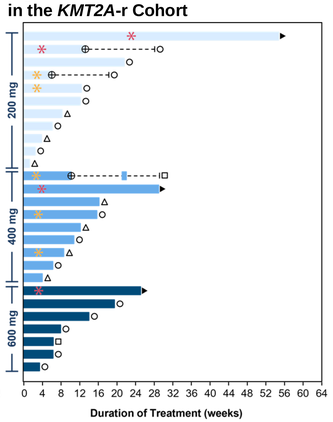


Figure 3. Duration of Treatment in the *KMT2A*-r Cohort



AE, adverse event; CR, complete remission; CRh, complete remission with partial hematological recovery; CRi, complete remission with incomplete hematological recovery; HSCT, hematopoietic stem cell transplant; MLFS, morphologic leukemia-free state.

- Time to absolute neutrophil count and platelet count recovery among responders with CRc are shown in **Table 6**

Table 6. ANC and Platelet Recovery in CRc Responders

Median (range)	*NPM1*-m and *KMT2A*-r		
	200 mg n=6	400 mg n=4	600 mg n=5
Days to ANC ≥0.5 x 10^9/L, Cycle 1	34 (28–66)	38 (35–50)	35 (29–42)
Days to ANC ≥1.0 x 10^9/L, Cycle 1	46 (28–137)	46 (37–54)	42 (34–43)
Days to Platelets ≥50 x 10^9/L, Cycle 1[a]	20 (0–76)	38 (0–84)	14 (0–29)
Days to Platelets ≥100 x 10^9/L, Cycle 1[a]	46 (0–61)	37 (22–84)	13 (0–35)

[a]*Includes 4 NPM1-m patients (200 mg n=1, 400 mg n=1, 600 mg n=2) with platelet counts that were never below 50 x 10^9/L.*
ANC, absolute neutrophil count; CRc, composite complete remission.

CONCLUSIONS

- In the ongoing KOMET-007 study, ziftomenib combined with VEN/azacitidine was well tolerated at all dose levels tested and continues to demonstrate promising clinical activity in R/R *NPM1*-m and *KMT2A*-r AML
- Ziftomenib combination therapy was well tolerated
  - No DLTs or ziftomenib-induced QTc prolongation were reported
  - On-target DS occurred in 8% of patients receiving ziftomenib (4/53; all Grade 2 or 3), including in 3 *KMT2A*-r patients and 1 *NPM1*-m patient; all patients had resolution of DS with appropriate management
- Clinical activity was demonstrated in *NPM1*-m and *KMT2A*-r R/R AML, including VEN-experienced patients
  - In the *NPM1*-m response-evaluable population, ORR was 68% and CRc was 50%
  - In *NPM1*-m patients with VEN exposure, ORR was 50% and CRc was 36%
  - In *KMT2A*-r patients, approximately one-third of patients responded, including those with prior VEN exposure
- Based on these encouraging initial results, a dose-expansion phase evaluating this triplet combination is underway in newly diagnosed and R/R *NPM1*-m and *KMT2A*-r AML patients

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