ZIFTOMENIB COMBINED WITH INTENSIVE INDUCTION CHEMOTHERAPY (7+3) IN NEWLY DIAGNOSED *NPM1*-M OR *KMT2A*-R ACUTE MYELOID LEUKEMIA: UPDATED PHASE 1A/B RESULTS FROM KOMET-007

AML-732

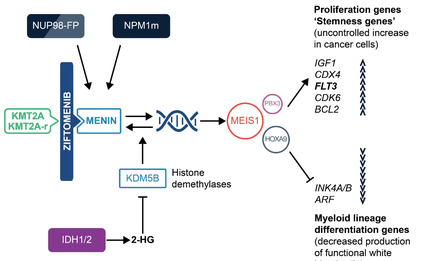
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Background

- *NPM1*-m and *KMT2A*-r drive leukemogenesis in ~35–40% of AML[1,2]
- **Ziftomenib** is a potent, highly selective, oral, investigational menin inhibitor with clinical activity as both monotherapy and in combination for adults with *NPM1*-m or *KMT2A*-r AML (**Figure 1**)[3,4]
- KOMET-007 (NCT05735184) is an ongoing dose-escalation (phase 1a) and expansion (phase 1b) study of ziftomenib in combination with venetoclax/azacitidine, venetoclax alone, or cytarabine and daunorubicin (7+3) in *NPM1*-m or *KMT2A*-r AML

Figure 1. Ziftomenib mechanism of action[5–14]

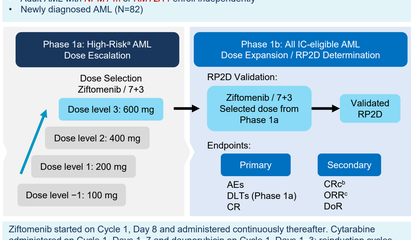


Aim

- Here we present updated safety and clinical activity in adults with newly diagnosed AML treated at the ziftomenib RP2D of 600 mg QD in combination with standard doses of 7+3 across phase 1a/b (**Figure 2**)

Methods

Figure 2. KOMET-007 study design



Ziftomenib started on Cycle 1, Day 8 and administered continuously thereafter. Cytarabine administered on Cycle 1, Days 1–7 and daunorubicin on Cycle 1, Days 1–3; reinduction cycles allowed based on bone marrow biopsy results.

[a]High-risk defined as *KMT2A*-r AML, or *NPM1*-m with adverse-risk cytogenetics per ELN criteria, age ≥60 years, and/or treatment-related AML regardless of age. [b]CR, CRh, or CRi. [c]CRc or MLFS.

Results

- As of March 21, 2025, 82 patients (49 *NPM1*-m; 33 *KMT2A*-r) were enrolled and treated (**Table 1**)
- Any grade and grade ≥3 TEAEs are shown in **Table 2**
- 29 patients (35%) had grade ≥3 ziftomenib-related AEs, most commonly (≥10%) febrile neutropenia (15%), platelet count decreased (15%), anemia (11%), and neutrophil count decreased (11%)
  - 1 case of DS (*KMT2A*-r, grade 3), which was successfully managed
  - 2 cases of investigator-assessed QTc prolongation (both *KMT2A*-r, grade 3). Both patients were on other medications (posaconazole and/or piperacillin/tazobactam) at time of QT assessment
- Clinical activity in response-evaluable patients is shown in **Table 3**
- For *NPM1*-m patients, median duration of CR and median OS were not reached; 2 patients received HSCT; 3 patients discontinued due to relapse (**Figure 3A**)
- For *KMT2A*-r patients, median duration of CR was 25.6 weeks (95% CI 8.3–NE), and median OS was not reached; 6 patients received HSCT (1 went onto ziftomenib maintenance); 1 patient discontinued due to an AE (**Figure 3B**)
- Median time to neutrophil and platelet recovery was comparable to that for intensive chemotherapy regimens[15-16]
  - ANC ≥1.0×10^9/L: 32 days (range 20–88)
  - Platelets (≥100×10^9/L): 29 days (range 20–63)

Results (continued)

Table 1. Baseline characteristics and patient disposition: 1L AML (N=82)

n (%)	*NPM1*-m (n=49)	*KMT2A*-r (n=33)	All Patients (N=82)
Age, median (range), years	60 (30–71)	43 (18–70)	56 (18–71)
Female	25 (51)	18 (55)	43 (52)
ECOG PS 0–1	43 (88)	31 (94)	74 (90)
Co-mutations			
FLT3[a]	6 (12)	5 (15)	11 (13)
IDH1/2	13 (27)	2 (6)	15 (18)
Therapy-related AML	2 (4)	8 (24)	10 (12)
Patients on treatment	35 (71)	25 (76)	60 (73)
Patients on study[b]	47 (96)	29 (88)	76 (93)
Follow-up, median (range), weeks	24.9 (4.3–47.1)	15.7 (1.1–40.3)	18.4 (1.1–47.1)

[a]*FLT3*-ITD allelic ratio <0.05 (3 *NPM1*-m) or considered ineligible for FLT3 inhibitor (3 *NPM1*-m, 5 *KMT2A*-r). [b]On treatment or in long-term follow-up.

Table 2. TEAEs and grade ≥3 TEAEs in all patients

n (%)	*NPM1*-m (n=49)	*KMT2A*-r (n=33)	All Patients (N=82)
Any grade (≥25% of all patients)	46 (94)	31 (94)	77 (94)
Febrile neutropenia	26 (53)	23 (70)	49 (60)
Diarrhea	22 (45)	17 (52)	39 (48)
Platelet count decreased	24 (49)	13 (39)	37 (45)
Pruritus	19 (39)	13 (39)	32 (39)
Nausea	18 (37)	8 (24)	26 (32)
Hypokalemia	16 (33)	10 (30)	26 (32)
Anemia	16 (33)	8 (24)	24 (29)
Stomatitis	12 (24)	12 (36)	24 (29)
ALT increased	13 (27)	9 (27)	22 (27)
Constipation	15 (31)	6 (18)	21 (26)
Grade ≥3 (≥10% of all patients)	42 (86)	29 (88)	71 (87)
Febrile neutropenia	25 (51)	20 (61)	45 (55)
Platelet count decreased	23 (47)	12 (36)	35 (43)
Anemia	16 (33)	8 (24)	24 (29)
Neutrophil count decreased	14 (29)	6 (18)	20 (24)
White blood cell count decreased	10 (20)	7 (21)	17 (21)
Sepsis	8 (16)	5 (15)	13 (16)
Lymphocyte count decreased	5 (10)	4 (12)	9 (11)

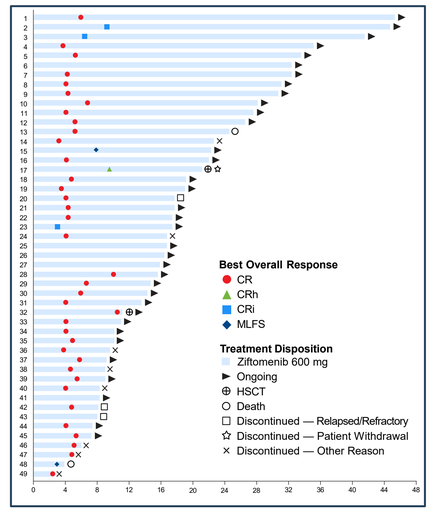
Table 3. Clinical activity in response-evaluable[a] 1L patients (N=71)

n (%)	*NPM1*-m (n=44)	*KMT2A*-r (n=27)	All Patients (N=71)
CRc	41 (93)	24 (89)	65 (92)
ORR	43 (98)	24 (89)	67 (94)
CR	37 (84)	20 (74)	57 (80)
CRh	1 (2)	0	1 (1)
CRi	3 (7)	4 (15)	7 (10)
MLFS	2 (5)	0	2 (3)
PR	0	0	0
NR	1 (2)	2 (7)	3 (4)
NE	0	1 (4)[b]	1 (1)
CR MRD-negativity, n/N (%)[c]	24/34 (71)	14/16 (88)	38/50 (76)
CRc MRD-negativity, n/N (%)[c]	26/38 (68)	15/18 (83)	41/56 (73)
Time to CR MRD-negativity, median (range), wks	4.7 (2–17)	4.4 (3–12)	4.5 (2–17)
Time to CRc MRD-negativity, median (range), wks	4.7 (2–17)	4.1 (3–12)	4.3 (2–17)

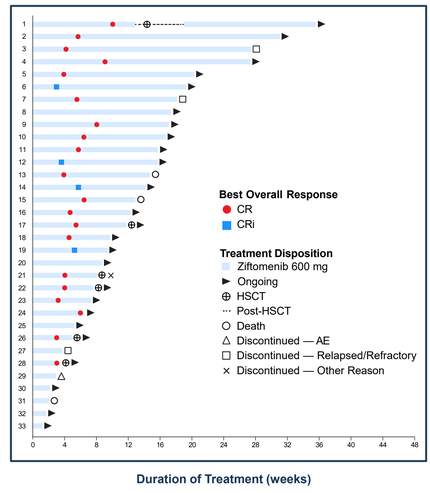
[a]Patients with ≥1 response assessment or who had died. [b]Patient had no response assessment and died before the data cut. [c]Among evaluable responders tested for MRD per local assay (NGS, RT-qPCR, FISH, flow cytometry). Preliminary central testing also shows concordance with local MRD-negativity rates.

Figure 3. Duration of treatment: 1L AML

(A) *NPM1*-m AML



(B) *KMT2A*-r AML



Conclusions

In the ongoing KOMET-007 study, ziftomenib 600 mg QD combined with 7+3 was well tolerated, with a safety profile consistent with previous reports

- Low rates of ziftomenib-related cytopenia and no additional myelosuppression were observed with the combination
  - Ziftomenib 600 mg QD did not delay neutrophil and platelet count recovery
- 1 case of grade 3 DS (*KMT2A*-r) which was successfully managed

Robust clinical activity with deep responses was demonstrated in newly diagnosed *NPM1*-m and *KMT2A*-r AML

- CRc rate: 93% for *NPM1*-m and 89% for *KMT2A*-r patients
  - CRc MRD negativity rate: 68% for *NPM1*-m at a median of 4.7 weeks, and 83% for *KMT2A*-r at a median of 4.1 weeks
- 96% (47/49) of *NPM1*-m and 88% (29/33) of *KMT2A*-r patients remained alive and continued on-study (median follow-up of 25 and 16 weeks, respectively)

Taken together, these data support the phase 3 advancement of this ziftomenib combination in newly diagnosed *NPM1*-m and *KMT2A*-r AML (KOMET-017)

Abbreviations
AE, adverse event; ALT, alanine aminotransferase; AML, acute myeloid leukemia; ANC, absolute neutrophil count; CI, confidence interval; CR, complete remission; CRc, composite complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; DLT, dose-limiting toxicity; DoR, duration of remission; DS, differentiation syndrome; ECOG PS, Eastern Cooperative Oncology Group performance status; ELN, European LeukemiaNet; HSCT, hematopoietic stem cell transplantation; IC, intensive chemotherapy; ITD, internal tandem duplication; *KMT2A-r, lysine methyltransferase 2A* rearrangements; MLFS, morphologic leukemia-free state; MRD, measurable residual disease; NE, not estimable or not evaluable; *NPM1*-m, *nucleophosmin 1* mutations; NR, no response; ORR, objective response rate; OS, overall survival; PR, partial remission; QD, once daily; QTc, corrected QT; RP2D, recommended phase 2 dose; TEAE, treatment-emergent adverse event

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