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Ziftomenib in relapsed/refractory *NPM1*-mutant acute myeloid leukemia: phase 1b/2 clinical activity and safety results from the pivotal KOMET-001 study

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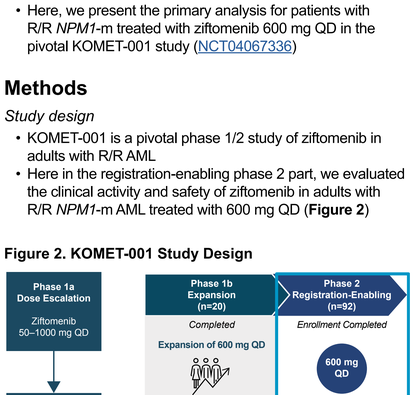
Background

- *NPM1*-m drives leukemogenesis in ~30% of AML cases[1]
- Despite current risk stratification, nearly half of patients will have R/R disease within a year, after which, outcomes are poor for high-risk patients, with <10% CR following venetoclax-based therapy[2-4]
- **Ziftomenib** – a potent, highly selective, oral, investigational menin inhibitor (**Figure 1**) – has shown clinical activity as monotherapy and in combination for adults with R/R *NPM1*-m and *KMT2A-r* AML, with 600 mg QD as the monotherapy RP2D for *NPM1*-m AML[5,6]

Figure 1. Ziftomenib Mechanism of Action[7-16]



Aim

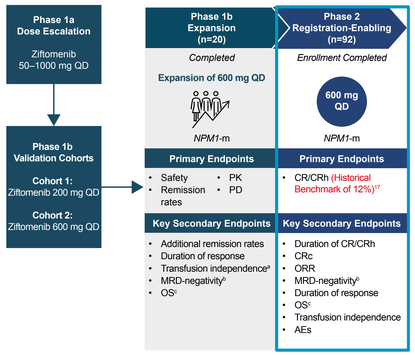
- Here, we present the primary analysis for patients with R/R *NPM1*-m treated with ziftomenib 600 mg QD in the pivotal KOMET-001 study (NCT04067336)

Methods

Study design

- KOMET-001 is a pivotal phase 1/2 study of ziftomenib in adults with R/R AML
- Here in the registration-enabling phase 2 part, we evaluated the clinical activity and safety of ziftomenib in adults with R/R *NPM1*-m AML treated with 600 mg QD (**Figure 2**)

Figure 2. KOMET-001 Study Design



[a]Defined as the absence of red blood cell and platelet transfusions for at least 56 consecutive days in the post-baseline period. [b]Defined as reaching at least one post-baseline MRD-negative result. [c]Defined as the time from the date of first dose to the date of death due to any cause.

Results

Patients

- From January 26, 2023 to May 13, 2024, patients were enrolled to the phase 2 study across 40 sites and 7 countries
- Pooled supportive analyses included 112 patients (92 from phase 2; 20 from phase 1b)
- As of the data cutoff date (December 20, 2024), 9 patients in the phase 2 part were receiving ziftomenib and 83 had discontinued due to progressive disease (n=34), AEs (n=17), lack of efficacy (n=12), patient withdrawal (n=8), death (n=3), or another reason (n=9)
- All 20 patients from phase 1b discontinued due to progressive disease (n=9), AEs (n=6), death (n=2), patient withdrawal (n=1), or another reason (n=2)
- Baseline characteristics were similar between the phase 2 and pooled phase 1b/2 populations (**Table 1**)

Table 1. Baseline Characteristics: R/R *NPM1*-m AML

	Ziftomenib RP2D 600 mg QD	
Characteristic, n (%)[a]	Phase 2 (N=92)	Pooled Phase 1b/2 (N=112)
Age, years, median (range)	**69 (33–84)**	**69 (22–86)**
18–64 years	33 (36)	42 (38)
≥65 years	59 (64)	70 (63)
Female	49 (53)	63 (56)
Race		
White	75 (82)	88 (79)
Non-White	17 (18)	24 (21)
Region		
United States/Canada	45 (49)	57 (51)
Europe	47 (51)	55 (49)
ECOG PS 0	27 (29)	30 (27)
1	49 (53)	63 (56)
2	16 (17)	19 (17)
Bone marrow aspirate blasts %, median (range)	39.5 (0.5–98)	44.0 (0.5–98)
Co-mutations, n/N[b] (%)		
FLT3-ITD	**38/84 (45)**	**43/102 (42)**
FLT3-TKD	**9/84 (11)**	**11/102 (11)**
IDH1-m	10/80 (13)	13/97 (13)
IDH2-m	16/81 (20)	22/96 (23)
Prior therapies, median (range)	2 (1–7)	2 (1–7)
1	32 (35)	37 (33)
2	30 (33)	37 (33)
≥3	30 (33)	38 (34)
Prior HSCT	22 (24)	26 (23)
Prior venetoclax	**54 (59)**	**67 (60)**
Prior menin inhibitor	1 (1)	1 (1)

[a]Unless otherwise specified. [b]Among patients with available co-mutation data at baseline.

Antitumor Activity

- **Primary phase 2 endpoint of CR/CRh was met (*P*-value=0.0058)* versus 12% historical control rate[17]**
- Response and duration of response are shown in **Table 2**
- For phase 2 patients, median time to CR/CRh (range) was **2.8 months** (1.0–15.0); median time to overall response was **1.9 months** (0.8–3.7)
- CR/CRh rates were comparable across prespecified subgroups, regardless of prior HSCT, venetoclax, or *FLT3*/*IDH* co-mutations (**Figure 3**)
- OS of the pooled phase 1b/2 population is shown in **Figure 4**
- TI in R/R *NPM1*-m AML patients is shown in **Figure 5**

*Based on primary analysis datacut (October 28, 2024).

Table 2. Response and Duration of Response: R/R *NPM1*-m AML

	Ziftomenib RP2D 600 mg QD	
	Phase 2 (N=92)	Pooled Phase 1b/2 (N=112)
CR/CRh, n (%)	**21 (23)**	**28 (25)**
Overall response, n (%)	**30 (33)**	**39 (35)**
CR	13 (14)	20 (18)
CRh	8 (9)	8 (7)
CRi/CRp	3 (3)	4 (4)
MLFS	5 (5)	6 (5)
PR	1 (1)	1 (1)
Other[a], n (%)	62 (67)	73 (65)
Duration of response, months, median (95% CI)		
CR/CRh	3.7 (1.9–NE)	3.7 (1.9–7.7)
CRc	4.6 (2.8–11.4)	5.1 (2.8–8.1)
ORR	4.6 (2.8–11.4)	4.6 (3.6–7.7)
Restricted mean duration of response[b], months (95% CI)		
CR/CRh	4.3 (3.1–5.6)	5.2 (3.6–6.7)
CRc	5.9 (4.0–7.7)	6.4 (4.6–8.1)
ORR	5.9 (4.4–7.5)	6.5 (4.9–8.1)
MRD negativity, n/N[c] (%)	**12/19 (63)**	**17/26 (65)**

[a]Stable disease/no response/clinical benefit/progressive disease/not evaluable. [b]Defined as the expected duration of response (area under the Kaplan-Meier curve, up to the time point when ≥10% of patients remain at risk). [c]Among CR/CRh responders evaluated for MRD (centrally tested).

Figure 3. Comparable CR/CRh Rates in Key Subgroups (Phase 2)

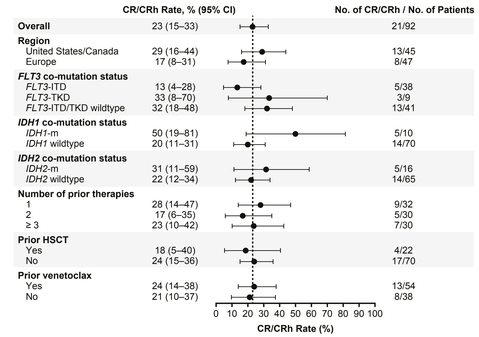
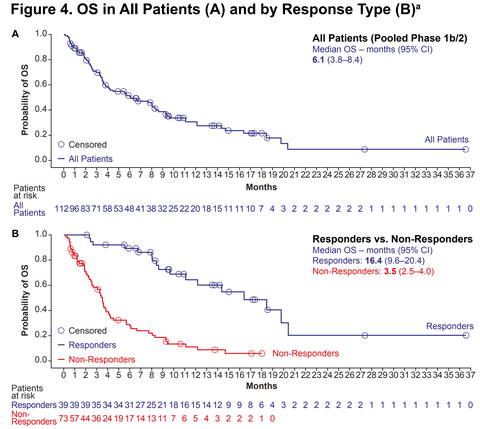
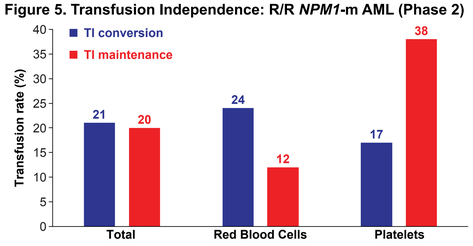


Figure 4. OS in All Patients (A) and by Response Type (B)[a]



[a]24 Patients remained alive at last follow-up, with 9 patients on-treatment.

Figure 5. Transfusion Independence: R/R *NPM1*-m AML (Phase 2)



	Total	Red Blood Cells	Platelets
TI conversion rate[a]	21% (17/82)	24% (18/75)	17% (12/71)
95% CI[b]	13–31	15–35	9–28
TI maintenance rate[c]	20% (2/10)	12% (2/17)	38% (8/21)
95% CI[b]	3–56	2–36	18–62

[a]Transfusion conversion rate was defined as the number of patients who were TD at baseline but became TI post-baseline divided by the total number of patients who were TD at baseline. [b]CI was calculated using the exact method based on binomial distribution. [c]Transfusion maintenance rate was defined as the number of patients who were TI at baseline and remain TI post-baseline divided by the total number of patients who were TI at baseline.
Post-baseline transfusion period was defined as the 29 days post first dose of ziftomenib until last dose before any new anticancer treatment (HSCT).

Safety and Tolerability

- Ziftomenib was well tolerated, with a safety profile consistent with previous studies,[5,6] including:
  - Low rates of ziftomenib-related myelosuppression
  - No clinically significant ziftomenib-associated QTc prolongation: 3 patients (3%): 1 Grade 2, 2 Grade 3 (all investigator-assessed). All 3 patients were also on additional medications associated with QTc prolongation (2 had electrolyte abnormalities, 1 had prior diagnosis of atrial fibrillation)
  - Manageable differentiation syndrome (15 [13%] had Grade 3 events; no Grade 4–5 events)
  - 3% of patients discontinued due to ziftomenib-related AEs
- All treatment-emergent AEs (any-cause) and ziftomenib-related AEs are shown in **Table 3**

Table 3. Treatment-Emergent (Any-Cause) and Treatment-Related AEs

	Ziftomenib RP2D 600 mg QD			
	Phase 2 (N=92)		Pooled Phase 1b/2 (N=112)	
AEs, n (%)	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any AE (≥ 20% of all patients)	92 (100)	86 (93)	112 (100)	105 (94)
Hematologic AEs				
Anemia	20 (22)	18 (20)	25 (22)	23 (21)
Febrile neutropenia	24 (26)	24 (26)	25 (22)	25 (22)
Thrombocytopenia	18 (20)	18 (20)	22 (20)	22 (20)
Nonhematologic AEs				
Diarrhea	27 (29)	1 (1)	36 (32)	5 (4)
Nausea	23 (25)	1 (1)	31 (28)	1 (1)
Hypokalemia	22 (24)	12 (13)	29 (26)	13 (12)
Differentiation syndrome	**23 (25)**	**14 (15)[a]**	**27 (24)**	**15 (13)[a]**
Pruritus	21 (23)	0	26 (23)	0
Peripheral edema	23 (25)	0	25 (22)	0
Pneumonia	19 (21)	13 (14)	24 (21)	17 (15)
Any ziftomenib-related AE in ≥ 5% of all patients	64 (70)	37 (40)	77 (69)	45 (40)
Hematologic AEs				
Anemia	5 (5)	5 (5)	6 (5)	6 (5)
Neutropenia	6 (7)	6 (7)	6 (5)	6 (5)
Nonhematologic AEs				
Differentiation syndrome	**22 (24)**	**14 (15)[a]**	**26 (23)**	**15 (13)[a]**
Pruritus	15 (16)	0	16 (14)	0
Nausea	8 (9)	0	13 (12)	0
Diarrhea	8 (9)	0	10 (9)	2 (2)
ALT increased	6 (7)	2 (2)	7 (6)	2 (2)
Decreased appetite	5 (5)	0	6 (5)	0

[a]No patients had Grade 4–5 differentiation syndrome.

Conclusions

In the pivotal KOMET-001 phase 2 study, the primary endpoint was met

- Ziftomenib achieved clinically meaningful, MRD-negative responses in this heavily pretreated R/R *NPM1*-m AML population
- Response rates were similar regardless of prior therapies received, including HSCT and venetoclax

Ziftomenib monotherapy was well tolerated with a safety profile consistent with previous studies[5,6]

- Low rates of ziftomenib-related myelosuppression
- 3% of patients discontinued due to ziftomenib-related AEs
- No clinically significant QTc prolongation was observed
- Differentiation syndrome was managed with protocol-specified mitigation strategies; there were no Grade 4–5 events

New drug application (NDA) submitted for ziftomenib monotherapy as a new potential treatment option for R/R *NPM1*-m AML

Ziftomenib combination studies are currently ongoing in both newly diagnosed and R/R AML (KOMET-007, KOMET-008)

Abbreviations

AE, adverse event; ALT, alanine aminotransferase; AML, acute myeloid leukemia; CR, complete remission; CR/CRh, complete remission with full or partial hematologic recovery; CRc, composite complete remission; CRh, complete remission with partial hematologic recovery; CRi/CRp, CR with incomplete hematologic or platelet recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, hematopoietic stem cell transplantation; ITD, internal tandem duplication; m, mutant; MLFS, morphologic leukemia-free state; MRD, measurable residual disease; NE, not estimable; ORR, overall response rate; OS, overall survival; PD, pharmacodynamics; PK, pharmacokinetics; QD, once daily; QTc, QT corrected; R/R, relapsed/refractory; RP2D, recommended phase 2 dose; TD, transfusion dependent; TI, transfusion independence; TKD, tyrosine kinase domain.

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