Abstract: LB2713

Title: ACTIVITY, TOLERABILITY, AND RESISTANCE PROFILE OF THE MENIN INHIBITOR ZIFTOMENIB IN ADULTS WITH RELAPSED/REFRACTORY NPM1-MUTATED AML

Abstract Type: Oral Presentation

Session Title: Late-Breaking Oral Session

Background:

The menin and histone-lysine-*N*-methyltransferase 2A (*KMT2A*) protein complex is an essential epigenetic regulator of genes critical for leukemogenesis in multiple leukemia subtypes, including in *NPM*1 mutant (*NPM1*m) acute myeloid leukemia (AML) and AML with *KMT2A* gene rearrangements (*KMT2A*r). The presence of co-mutations can portend a poor prognosis, particularly in the relapsed/refractory (R/R) setting, which is an area of high unmet need.

Aims:

The purpose of the Phase (Ph) 1 portion of KOMET-001 (NCT04067336) is to establish the safety and recommended phase 2 dose (RP2D) for ziftomenib monotherapy in *NPM1*m and *KMT2Ar* R/R AML.

Methods:

KOMET-001 (NCT04067336) is a global, open-label Ph 1/2 study of ziftomenib in adult patients (pts) with R/R AML. The Ph 1 dose escalation and randomized dose expansion portion in pts with *KMT2Ar* or *NPM1*m R/R AML is fully enrolled. Ziftomenib is dosed orally, once daily, in 28-day cycles until relapse, progression, or unacceptable toxicity.

Results:

This report provides an update on the Ph 1 *NPM1*m pts, with emphasis on those dosed at the 600mg RP2D (n=20) as of 12APR2023. Median age of RP2D pts was 70.5 years (22 to 86y). FLT3 (30%) and IDH1/2 (40%) co-mutations were common (20% had both co-mutations). Median number of prior therapies was 3.0 (r: 1 to 10); 20% had ≥1 prior stem cell transplant (SCT).

Based on updated results, the complete remission (CR) rate for *NPM1*m pts at 600mg is 35%, with 40% of pts overall achieving composite CR (CRc) and ORR of 45% (Table 1). The median time to first response is 51 days (r: 26 to 225). One CR at the 200mg dose has an ongoing DoR of 35 cycles. The median DoR for all *NPM*1m pts achieving CRc is 8.2 months (m) per Kaplan-Meier estimate (95% CI: 1.0 to NE). Two pts (1 CR and 1 CRi) underwent SCT and remain in remission as of the cutoff, one on post-SCT ziftomenib maintenance therapy. Molecular analyses suggest ziftomenib leads to measurable residual disease (MRD) clearance of target mutations such as *NPM*1, and co-mutations (eg, *FLT3* and *IDH1*) likely by targeting the founding clone and subclonal events or through targeting aberrant gene expression, as at least 2 pts with *FLT3* and *IDH1* co-mutations present at baseline were undetectable after 2 cycles.

Most pts (85%) had at least one ≥Gr 3 treatment-emergent adverse event (TEAE); 30% were potentially treatment-related. The most frequent (>20%) TEAEs ≥ Gr 3 were anemia (25%) and thrombocytopenia (20%). Any grade differentiation syndrome (DS) was reported in 20%; most (n=3) were Gr 2.

The resistance profile was explored and the resistance mutation MEN1-M327I was found to develop in 1 of 29 pts (3.4%), detected at C4D28; the pt maintained stable disease through cycle 7. One key new biochemical finding, confirmed by crystal structure, demonstrates that ziftomenib retains full activity against the T349M mutation, detected in two thirds of pts who acquired menin gatekeeper mutations on another recent menin inhibitor trial.

Summary/Conclusion:

Ziftomenib continues to demonstrate significant clinical activity in heavily pretreated and co-mutated R/R *NPM1*m AML pts where 35% of pts achieved CR. The safety profile remains consistent, and episodes of DS are clinically manageable. Data reveal that remissions are durable, with MRD clearance of *NPM1* and key co-mutations. Resistance mutations develop infrequently, and ziftomenib remains effective against a common menin gatekeeper mutation. A single-arm registration-directed Ph 2 study is currently accruing to further evaluate ziftomenib monotherapy in R/R NPM1m AML.

CR Rate	
n (%)	**7 (35)**
95% (CI)	**(15.4, 59.2)**
CR/CRh Rate	
n (%)	**7 (35)**
95% (CI)	**(15.4, 59.2)**
CRc Rate (CR+CRh+CRi)	
n (%)	**8 (40)**
95% (CI)	**(19.1, 63.9)**
MRD Negativity Rate[1]	
n (%)	**4 (50)**
95% (CI)	**(15.7, 84.3)**
ORR Rate (CR+CRh+CRi+MLFS)	
n (%)	**9 (45)**
95% (CI)	**(23.1, 68.5)**

[1]Six of 8 patients achieving CRc were evaluated for MRD. Of those evaluated, 66.7% were MRD negative.

Table 1: Responses to treatment with ziftomenib