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P504 UPDATED DATA FOR ZIFTOMENIB IN PATIENTS WITH NPM1-MUTATED RELAPSED OR REFRACTORY ACUTE MYELOID LEUKEMIA

Topic: 4. Acute myeloid leukemia - Clinical

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Background:

The menin and histone-lysine-*N*-methyltransferase 2A (*KMT2A*) protein complex is an essential epigenetic regulator of genes critical for maintenance of multiple genetic subtypes of leukemia. This complex is implicated in NPM1 mutant acute myeloid leukemia (AML) (*NPM*1m, 25-30% of AML) as well as AML with *KMT2A* gene rearrangements (*KMT2A*r; 5-10% of AMLs). The presence of co-mutations in genes such as *IDH1/2* and *FLT3* portend a poor prognosis, particularly in the relapsed/refractory (R/R) setting. There is high unmet need for the development of agents able to address these patient populations.

Aims:

The purpose of the Phase (Ph) 1 portion of KOMET-001 (NCT04067336) is to establish the safety, tolerability, and recommended phase 2 dose (RP2D) for ziftomenib monotherapy in *NPM1*–m and *KMT2A*–r R/R AML.

Methods:

KOMET-001 is a global, open-label Ph 1/2 study of ziftomenib in adult patients (pts) with R/R AML. The dose escalation and randomized, multi-dose expansion in pts with *KMT2A*r or *NPM1*m R/R AML is fully enrolled. The single-arm Ph2 registration-enabling portion evaluating the ziftomenib monotherapy RP2D in pts with R/R *NPM1*m AML is currently enrolling. Ziftomenib is dosed orally, once daily, in 28-day cycles until relapse, progression, or unacceptable toxicity.

Results:

This report provides updates on the Ph 1 *NPM1*m pts dosed at the 600mg RP2D (n=20) and on duration of remission (DoR) for a 200mg pt as of 31JAN2023. The median age for pts treated at RP2D was 70.5 years (22 to 86y). FLT3 and IDH1/2 mutations were common (35% FLT3, 30% IDH1/2, and 20% both co-mutations). Median number of prior therapies was 2.5 (r: 1 to 8), including 15% with ≥1 prior stem cell transplant (SCT) and 60% with prior venetoclax.

The cumulative safety profile for the ziftomenib RP2D is consistent with prior reports. Most (85%) had at least one ≥Gr 3 treatment-emergent adverse event (TEAE), with 30% of TEAEs considered potentially treatment-related. The most frequent (>10%) TEAEs ≥ Gr 3 were anemia (25%), pneumonia (20%), thrombocytopenia, neutropenia and hyperglycemia (15% each). Any grade differentiation syndrome (DS) was reported in 20%; 5% (n=1) as Gr 3.

As of 31JAN2023, the complete remission (CR) rate for *NPM1*m pts treated with 600mg was 30%, composite CR rate (CRc) was 35%, and ORR rate was 40% (see Table 1). The median DoR for pts achieving CRc, which continues to mature, was 8.2 months (m) per Kaplan-Meier estimate (95% CI: 1.5 to NE). One CR was noted at the 200mg dose with an ongoing DoR of 32 cycles. Median time to CR was 70 days (r: 26 to 89). Two pts (1 CR and 1 CR with incomplete hematologic recovery [CRi]) proceeded to SCT and both remain in remission as of the cutoff. Median overall survival for *NPM1*m pts treated with 600mg was 5.1m (95% CI: 2.1 to NE), with a median duration of follow-up of 8.0m. At the cutoff, 57.1% of pts achieving CRc at RP2D remain on treatment or in post-SCT follow-up; those on treatment continue to show evidence of evolving responses.

Summary/Conclusion:

Ziftomenib continues to demonstrate significant clinical activity in heavily pretreated and co-mutated R/R *NPM1*m AML pts. The safety profile remains consistent and the on-target effect of DS continues to be manageable. Data suggest durable remissions as the DoR continues to mature with 5 of 8 pts with CRc ongoing at the cutoff. A single-arm registration-directed Ph 2 study is currently accruing to further evaluate ziftomenib monotherapy in R/R *NPM1*m AML.

Table 1. Response Rates for *NPM1*-m Patients treated at the Ziftomenib RP2D

CR Rate	
n (%)	**6 (30)**
95% (CI)	**(12, 54)**
CR/CRh Rate	
n (%)	**6 (30)**
95% (CI)	**(12, 54)**
CRc Rate (CR+CRh+CRi)	
n (%)	**7 (35)**
95% (CI)	**(15, 59)**
MRD Negativity Rate[1]	
n (%)	**3 (43)**
95% (CI)	**(10, 82)**
ORR Rate (CR+CRh+CRi+MLFS)	
n (%)	**8 (40)**
95% (CI)	**(19, 64)**

[1]Five of 7 patients achieving CRc were evaluated for MRD. Of those evaluated, 60% were MRD negative.