Abstract: S134

Title: PHASE 1B STUDY OF AZACITIDINE, VENETOCLAX AND REVUMENIB IN NEWLY DIAGNOSED OLDER ADULTS WITH NPM1 MUTATED OR KMT2A REARRANGED AML: INTERIM RESULTS OF DOSE ESCALATION FROM THE BEATAML CONSORTIUM

Abstract Type: Oral Presentation

Session Title: Acute myeloid leukemia - Clinical 1 - Menin inhibitor

Background:

Although Azacitidine + Venetoclax (Aza/Ven) is an important treatment advancement for newly diagnosed (ND) unfit acute myeloid leukemia (AML) patients, long-term outcomes remain poor. Menin inhibitors are a new class of investigational targeted therapies that have promising clinical activity in patients (pts) with *NPM1*-mutated (*NPM1*m) or *KMT2A*-rearranged (*KMT2A*r) AML, both of which rely on the interaction of menin with KMT2A and subsequent aberrant up-regulation of HOX/MEIS-related genes. Revumenib (Rev) is an oral menin inhibitor studied as a single agent in relapsed/refractory *NPM1*m or *KMT2A*r AML with an overall response rate of 53%. We hypothesized that the addition of Rev to Aza/Ven would be safe and effective in ND *NPM1*m or *KMT2A*r AML. Here we report the interim results of a phase 1b dose escalation study of Aza/Ven/Rev from the Beat AML Master Trial (ClinicalTrials.gov NCT03013998).

Aims:

To establish the recommended dose of Rev + Aza/Ven and evaluate safety in ND older pts with*NPM1*m or *KMT2A*r AML.

Methods:

As part of the Beat AML Master Trial, ND pts ≥60 years were screened and assigned this sub-study if they had *NPM1*m or *KMT2A*r AML. A 3+3 design identifying dose-limiting toxicities (DLT) was used to determine the recommended dose of Rev in combination with Aza/Ven (Aza: 75 mg/m2, days 1-7; Ven: 400mg dose-adjusted, days 1-28). All pts were required to take an azole with strong CYP3A4 inhibition for cycle 1. Two dose levels (DL) of Rev (days 1-28) were investigated: DL1a: Rev 113 mg PO Q12hours; DL2a: Rev 163 mg PO Q12hours. DLTs were assessed during cycle 1 and defined as non-hematologic: drug-related Grade (G) ≥3 toxicity, or hematologic: neutrophil count <500/μL and platelets <25,000/μL ≥42 days from start of cycle 1 in absence of AML.

Results:

Characteristics of pts enrolled on DL1a and DL2a are shown in Table 1. Seven pts enrolled on DL1a and 6 were DLT evaluable. There was only 1 hematologic DLT in DL1a. Subsequently, 6 pts were enrolled and evaluable in DL2a where there were no DLTs. Overall, differentiation syndrome (DS) was seen in 4 (31%) pts with 1 G3 DS requiring temporary treatment interruption for 10 days, with subsequent Rev resumption at the same dose. QTcF prolongation was seen in 5 (38%) pts (G3: n=2). Overall, treatment-related G3 toxicities were rare (febrile neutropenia: n=2; diarrhea: n=1; sepsis: n=1; pulmonary edema: n=1; acute kidney injury: n=1; decreased appetite: n=1).

Ten pts achieved a complete remission (CR), while 3 additional pts achieved CR with partial hematologic recovery (CRh: n=1), and CR incomplete recovery (CRi: n=2) for a composite CR (cCR) of 100% (95% CI: 75.3-100) (Table 2). Of the 12 pts tested by centralized flow cytometry (sensitivity of .01%) none had measurable residual disease. With a median follow-up of 7.6 months (range: 1.8-14.7), there were two deaths following treatment discontinuation at 13.5 months (DL1a) and 3.0 months (DL2a). Five pts (DL1a: 3; DL2a: 2) remain on study while 8 pts discontinued treatment due to relapse (n=2), adverse events (cytopenias: n=2, sepsis: n=2), and allogeneic stem cell transplant (n=2).

Summary/Conclusion:

In this phase 1b study, Aza/Ven/Rev was safely administered to ND older adults with*NPM1*m or *KMT2A*r AML without a maximal tolerated dose. The interim results revealed a cCR rate of 100% in the dose escalation phase (n=13). The study is currently enrolling pts on a randomized expansion phase comparing DL1a to DL2a to determine the optimal dose of Aza/Ven/Rev. Updated clinical results will be presented at the meeting. These data support the continued development of Aza/Ven/Rev in ND AML

Table 1: Baseline Characteristic	**DL1a (n=7)**	**DL2a (n=6)**	**All (n=13)**
Age, years, Median (range)	67 (61-85)	74.5 (65.0-84.0)	73 (61-85)
Age ≥ 75 years, no. (%)	3 (42.9)	3 (50.0)	6 (46.2)
Female	6 (85.7)	1 (16.7)	7 (53.9)
Performance Status, no. (%)			
0	0 (0.0)	1 (16.7)	1 (7.7)
1	5 (71.4)	2 (33.3)	7 (53.9)
2	2 (28.6)	3 (50.0)	5 (38.5)
WBC, 10^3/uL, Median (range)	5.2 (1.5-13.3)	2.5 (1.5-8.6)	2.5 (1.5-13.3)
Bone Marrow Blasts (%)	67 (19-90)	63 (53-82)	65 (19-90)
KMT2A rearranged, no. (%)[#]	3 (42.9)	2 (33.3)	5 (38.5)
*NPM1*m, no. (%)*	4 (57.1)	4 (66.7)	8 (61.5)

[#]Confirmed locally by FISH/Cytogenetics; *Confirmed centrally.

Table 2: Outcomes	**DL1a (n=7)**	**DL2a (n=6)**	**All (n=13)**
Best Response, no. (%)			
CR	5 (71.4)	5 (83.3)	10 (76.9)
CRh	0 (0.0)	1 (16.7)	1 (7.7)
CRi	2 (28.6)	0 (0.0)	2 (15.4)
Composite CR Rate			
CR/CRh/CRi, no. (%, 95% CI)	7 (100, 59.0-100)	6 (100, 54.0-100)	13 (100, 75.3-100)
12 Month Survival Estimate, (95% CI)	100 (100-100)	66.7 (5.4-94.5)	90.0 (47.3-96.5)
Measurable Residual Disease Neg, no. (%)	6 (86)	6 (100)	12 (92)
Relapse, no. (%)	1 (14)	1 (17)	2 (15)
Allogeneic Stem Cell Transplant, no. (%)	1 (14)	1 (17)	2 (15)

Keywords: KMT2A, Acute myeloid leukemia, Clinical trial, MLL