Abstract: S133

Title: A PHASE 1B STUDY OF THE MENIN-KMT2A INHIBITOR JNJ-75276617 IN COMBINATION WITH VENETOCLAX AND AZACITIDINE IN RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA WITH ALTERATIONS IN KMT2A OR NPM1

Abstract Type: Oral Presentation

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

Background:

Relapsed/refractory (RR) AML with *KMT2A* alterations or *NPM1* mutations (*NPM1*m) are associated with poor outcomes. The interaction between the scaffolding protein menin and methyltransferase KMT2A is essential for orchestrating leukemic gene expression and uncontrolled cell proliferation in *KMT2A*-altered and *NPM1*m AML. JNJ-75276617 is a potent and selective inhibitor of the menin-KMT2A interaction. A phase 1 study (NCT04811560) with JNJ-75276617 reported single agent activity in RR acute leukemia harboring *KMT2A* or *NPM1* alterations. Preclinical studies have shown synergistic antiproliferative effects of JNJ-75276617 in combination with venetoclax (VEN) + azacitidine (AZA) in *KMT2A*-* and *NPM1*-altered AML.

Aims:

To determine safety and preliminary clinical activity of JNJ-75276617 in combination with VEN + AZA in adult participants (pts) with RR AML harboring *KMT2A* or *NPM1* alterations.

Methods:

NCT05453903 is an** ongoing Phase 1b, multicenter, dose-finding study. Written informed consent was obtained from all pts. As of 05 February 2024, oral JNJ-75276617 was given at doses ≥15 mg BID starting at Day 4 continuously in combination with VEN (28-day cycle) + AZA (7 days/cycle) according to the label. AEs were graded by CTCAE v5.0. Responses were investigator-assessed per modified ELN2017 criteria. The safety dataset (n=45) includes pts who received at least one dose of study therapy. The efficacy dataset (n=21) is focused on pts with *NPM1*m or *KMT2A*-rearranged (*KMT2A*r) AML at dose levels ≥50 mg BID. Efficacy in other *KMT2A* alterations (amplifications and partial tandem duplications) is still being explored.

Results:

In the safety dataset, 45 pts received JNJ-75276617 in combination with VEN+AZA. Median age was 60 [20-82] yrs; 51% *NPM1*m, 49% *KMT2A* altered; median prior lines of therapy was 2 [1-5], including 56% (25/45) with prior VEN exposure and 27% (12/45) with prior allograft.

Overall, 87% (39/45) of pts experienced ≥1 treatment-related AE (TRAE) attributed to any study treatment (all grades); nausea (38%), vomiting (31%), and thrombocytopenia (31%) were the most common. Grade ≥3 TRAEs were observed in 60% (27/45) of pts; most common were thrombocytopenia (29%), leukopenia (24%), neutropenia (22%) and febrile neutropenia (22%). TRAEs (any grade) attributed solely to JNJ-75276617 were observed in 22% (10/45) of pts; most frequently Grade ≤2 GI events (7%) and one Grade 3 hyperkalemia (2%). No differentiation syndrome (DS), QTcF prolongation, tumor lysis syndrome (TLS) or DLTs were reported.

In the efficacy dataset at dose levels ≥50 mg BID of JNJ-75276617, ORR (≥PR) was 86% (18/21); CR/CRh/CRi (composite CR; cCR) 48% (10/21); CR/CRh 24% (5/21). ORR was similar across genetic profiles. For pts with prior VEN exposure, ORR was 82% (9/11); cCR 36% (4/11); CR/CRh 18% (2/11). Median time to first response in the efficacy dataset was 23 [14, 59] days; median time to cCR was 52 [14, 100] days.

Across all dose escalation cohorts (n=45), 9 responders discontinued treatment and proceeded to allograft and 11 additional pts remain on active treatment, including one pt on study treatment for >12 months.

Summary/Conclusion:

In this first analysis of a Phase 1b study exploring the triplet combination of JNJ-75276617+VEN+AZA in RR *KMT2A*-altered and *NPM1*m AML, the safety profile has been acceptable, with no DLTs observed and the RP2D(s) yet to be determined. To date, no AEs of DS, QTcF prolongation or TLS have been reported. Preliminary antileukemic efficacy with this triplet combination in RR AML was demonstrated, including in pts previously exposed to VEN.

Keywords: Acute myeloid leukemia, KMT2A, Targeted therapy