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ORAL ABSTRACTS

616.ACUTE MYELOID LEUKEMIAS: INVESTIGATIONAL THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

A First-in-Human Phase 1 Study of the Menin-KMT2A (MLL1) Inhibitor JNJ-75276617 in Adult Patients with Relapsed/Refractory Acute Leukemia Harboring *KMT2A* or *NPM1* Alterations

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Background: Relapsed/refractory (R/R)acute leukemia withalterations in *KMT2A* (also called *MLL1*; 9-15% of adult AML, 10% of ALL) or *NPM1* (30% of adult AML) are often associated with poor outcomes. Pre-clinical studies demonstrated the relevance of the menin-KMT2A protein-protein interaction in sustaining leukemic cells with *KMT2A* and *NPM1* alterations (Kuhn 2016). JNJ-75276617 is a potent and selective inhibitor of the interaction between the scaffolding protein menin and the methyltransferase KMT2A with preclinical activity in *KMT2A*-rearranged or *NPM1*-mutated leukemic cell lines and primary leukemia patient samples *in vitro* and *in vivo* (Kwon 2022). We report initial data investigating JNJ-75276617 in adult participants (pts) with R/R acute leukemia harboring *KMT2A* alterations (rearrangements, amplifications, or partial tandem duplications) or *NPM1* mutations.

Methods: 75276617ALE1001 (NCT04811560) is an ongoing Phase 1, multicenter, open-label, dose-finding study. Pts in dose escalation receive JNJ-75276617 orally on a 28-day cycle. As of 8 April 2023, multiple dose levels ≥15 mg have been explored on either a daily or twice daily (BID) dosing schedule. AEs were graded by CTCAE v5.0. Responses were investigator-assessed per ELN2017. Preliminary safety, efficacy and PD data are reported herein, with a focused review of the efficacy in higher dose levels with ≥3 pts dosed.

Results: Fifty-eight pts received JNJ-75276617. The median age was 63 (range: 19-83) years; 56 pts (97%) had R/R AML and 2 (3%) had R/R ALL. The median number of prior lines of treatment was 2 (range: 1-7), including 10 (17%) pts with a prior allogeneic stem cell transplant. A *KMT2A* or *NPM1* alteration was present in 33 (57%) and 25 (43%) pts, respectively.

Thirty (52%) pts experienced ≥1 treatment-related AE (TRAE); most commonly differentiation syndrome (DS) (8 [14%]). Grade ≥3 TRAEs were observed in 17 (29%) pts; those reported in ≥2 pts were neutropenia (6 [10%]), anemia and thrombocytopenia (4 [7%] each), DS (3 [5%]), and ALT and AST increase (2 [3%] each). Dose limiting toxicities (DLTs) were observed in 5 (9%) pts, with DS (2 [3%]) as the only DLT reported in ≥2 pts.

In 26 (63%) of the 41 pts with disease evaluation data, there was a reduction in bone marrow (BM) disease burden (*Figure 1*). Of these, a ≥50% decrease in BM blasts was observed in 16 (39%) pts. In the highest dose level with ≥3 pts (90 mg BID; n=8), the ORR (≥PR) was 50% (n=4), with all responders ongoing (*Figure 2*). These responders (2 *NPM1*-, 2 *KMT2A*-altered) achieved CR (1 pt), CRh (1 pt), and CRi (2 pts). In a review of higher dose levels with ≥3 pts (≥45 mg BID; n=20), the ORR was 40% (n=8), with 7 responders ongoing (*Figure 2*). These responders (5 *NPM1*-, 3 *KMT2A*-altered) achieved CR (3 pts), CRh (1 pt), CRi (3 pts), and PR (1 pt); median (range) time to first response (≥PR) 1.81 mos (1.0-3.3; n=8); time to CR, CRh, or CRi 1.77 mos (1.0-3.3; n=7); and time to CR 2.79 mos (1.8-2.9; n=3). Across all cohorts there were 12 responders, including 1 MRD negative CR. One responder discontinued treatment for allogeneic transplant; however, 8 responders continue on treatment, including 2 pts in cycle 9.

Preliminary PD data from unfractionated BM and/or PBMCs in paired samples among responders (n=12) show biologic activity as indicated by reduction in expression (mean fold change from baseline calculated as [on-tx-baseline]/baseline [range]) of menin-KMT2A target genes (*MEIS1* -0.42 [-1.0-9.0]; *HOXA9* -0.03 [-1.0-21.7]; *FLT3* 18.6 [-1.0-425]) and induction of genes associated with differentiation (*ITGAM* 55.0 [-0.93-1467]; *MNDA* 5.9 [-1.0-83.5]). Compared to baseline, the percentage of *KMT2A*-altered cells or *NPM1* variant allele frequency (VAF) was reduced in responders, with a decrease in *KMT2A*-altered cells by break-apart FISH probe from 59.2% at baseline to 8.1% post-treatment and in *NPM1* VAF using a myeloid gene NGS panel from 13.1% at baseline to 2.8% post-treatment.

Conclusions: Dose escalation in 75276617ALE1001 is ongoing with the RP2D(s) yet to be determined. Pts in dose expansion will receive JNJ-75276617 at the identified RP2D(s). Preliminary results of this FIH Phase 1 study demonstrate that JNJ-75276617 monotherapy has an acceptable safety profile, encouraging antileukemic activity, and emerging biologic activity consistent with the proposed mechanism of action in pts with R/R acute leukemia harboring *KMT2A* or *NPM1* alterations.

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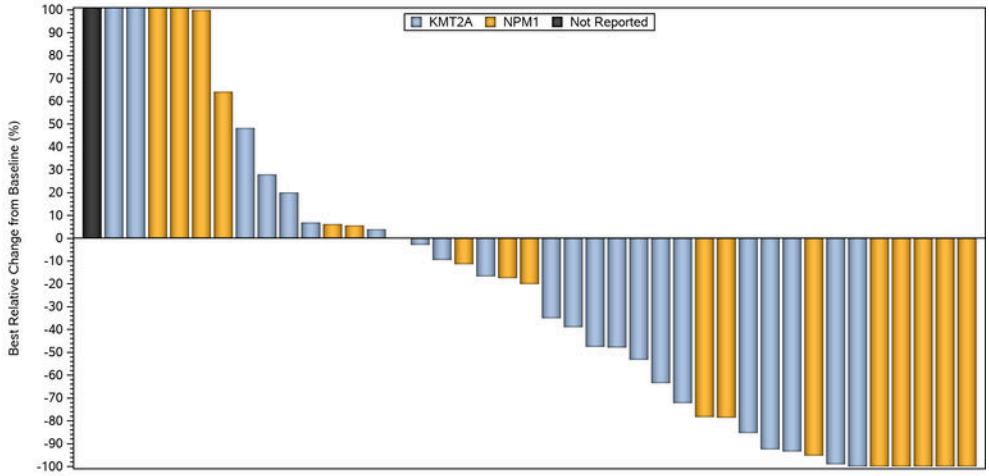
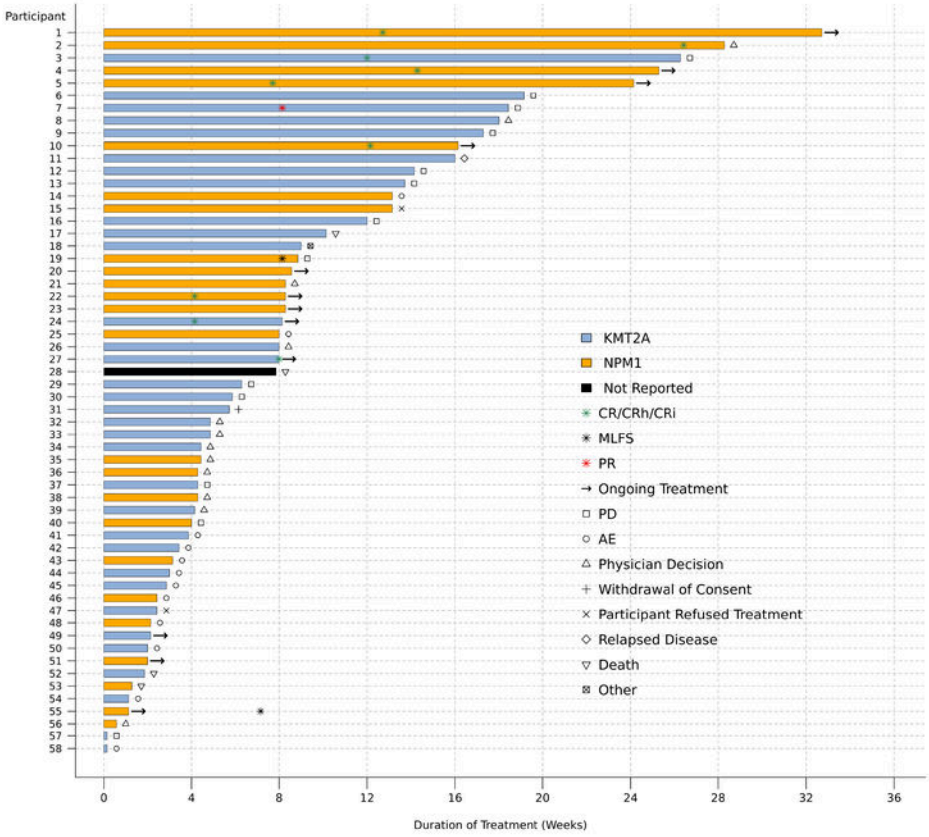
Figure 1. Best Percent Change from Baseline in Bone Marrow Blasts With JNJ-75276617 Monotherapy in R/R Acute Leukemia



Note: Bars are only presented for participants where a measurable change from baseline is found in the data (n=41; 23 *KMT2A*-altered, 17 *NPM1*-altered, 1 Not Reported).
Note: Each bar represents a unique study participant.
Note: One participant did not have *NPM1* or *KMT2A* mutation reported as of data-cut.
Note: Five participants had best relative change from baseline of >100%.

Figure 2. Preliminary Clinical Activity of JNJ-75276617 Monotherapy in R/R Acute Leukemia



Key: CR=Complete Response; CRh=CR with Partial Hematologic Recovery; CRi=CR with Incomplete Hematologic Recovery; MLFS=Morphologic Leukemia-Free State; PR=Partial Remission; PD=Progressive Disease; AE=Adverse Event
Note: Participant 2 was sent for transplant after discontinuing treatment.
Note: Participant 28 did not have *NPM1* or *KMT2A* mutation reported as of data-cut.
Note: Participant 55 had incomplete duration of treatment information entered at time of data-cut.

Figure 1

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