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

Alrizomadlin (APG-115) Alone or Combined with Azacitidine (AZA) in Patients (pts) with Relapsed or Refractory (R/R) Acute Myeloid Leukemia (AML) or Relapsed or Progressive Higher-Risk Myelodysplastic Syndrome (HR-MDS): Phase 1b Trial Results

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Background

Pts with R/R AML and HR-MDS failing hypomethylating agents have limited therapeutic options and relatively dismal outcomes with available therapies. Investigational alrizomadlin is a novel, orally active, potent, small-molecule selective inhibitor that destabilizes the p53-MDM2 complex and activates p53-mediated apoptosis in tumor cells and has shown apoptotic activity in AML and MDS xenograft models, alone and combined with AZA. Here, we present safety and efficacy results of this therapy in these pts.

Methods

This open-label dose escalation and expansion trial included adults with R/R AML or relapsed/progressed HR-MDS (IPSS-R $\geq$ 4.5). MTD and RP2D of alrizomadlin ± AZA were determined by dose escalation. Alrizomadlin (100/150/200/250 mg) was administered orally on Days (D) 1-7 in 28-day cycles. In the combination dose escalation group, alrizomadlin (100/150/200 mg) + AZA (75 mg/m ^{2}) was administered orally once daily on D 1-7 in 28-day cycles and at the combination RP2D during dose expansion. Responses were assessed per revised International Working Group (IWG) Response Criteria 2003, ELN 2017 classifications for AML, and IWG 2006 for MDS. Extensive pharmacokinetic (PK) analyses were performed.

Results

As of June 1, 2023, 29 pts were enrolled in China. In the monotherapy group, 21 pts (median [range] age, 65 [32-76] years; 76.2%, R/R AML) had a median (range) of 2 (1-10) prior lines of therapy. In the combination group, 8 pts (median [range] age

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of 69.5 [20-76] years; 50%, R/R AML) had a median (range) of 2 (1-4) prior lines of therapy. In both groups, common any-grade treatment-related adverse events (TRAEs; ≥ 20%) were hematologic- and gastrointestinal-related toxicities, hypokalemia, and dizziness, and most grade ≥ 3 TRAEs were hematologic toxicities. No grade ≥ 3 gastrointestinal toxicities were reported (Figure 1). One DLT, a pulmonary embolism (PE), was reported among 6 evaluable patients at the alrizomadlin 100 mg + AZA dose level: a 59-year-old pt with MDS had a prior COVID-19 infection and abnormal coagulation function before (and during) study treatment. The study investigator attributed the PE to the pt's COVID-19 infection, age, primary disease, and long-term bed rest. One pt in each arm discontinued treatment because of AEs. In pts with AML, the overall response rate (ORR) was defined as complete remission (CR) + CR with incomplete hematologic recovery (CRi) + partial response (PR) + morphologic leukemia-free state (MLFS). In pts with MDS, ORR was defined as CR + PR + marrow CR (mCR). In the monotherapy group, the ORR and CR/CRi rates among pts with R/R AML were 25% (4/16) and 18.75% (3/16), respectively. Three of 6 pts with MDS that progressed to R/R AML experienced responses, including 2 CRis and 1 MLFS. One of 10 pts with R/R AML treated with venetoclax + HMA experienced a CRi. In the monotherapy cohort, 4 pts with MDS refractory to HMAs were evaluated, of whom 2 experienced an mCR. The monotherapy RP2D was determined as 200 mg. In the combination group, 6 pts had an efficacy evaluation at least once. Among these pts, 3 of 3 with MDS experienced an mCR and 1 of 3 with R/R AML, MLFS. Among 4 pts with prior venetoclax + HMA treatment, 2 with MDS experienced an mCR and 2 with R/R AML showed a half marrow blast reduction at the end of C1 (Table 1). No PK drug-drug interaction between alrizomadlin and AZA was observed.

Conclusions

Alrizomadlin alone or combined with AZA demonstrated a manageable safety profile and preliminary efficacy in pts with R/R AML and HMA-refractory MDS. An antileukemic effect was observed in both monotherapy and combination settings, including a few pts whose disease failed on prior venetoclax treatment. Evaluation of the alrizomadlin + AZA cohort is ongoing. Internal study (CT.gov) identifiers: APG-115-AC101 (NCT04275518).

Disclosures Chen: *Ascentage Pharma:* Current Employment, Current equity holder in publicly-traded company. **Yu:** *Ascentage Pharma:* Current Employment, Current equity holder in publicly-traded company. **Wang:** *Ascentage Pharma:* Current Employment, Current equity holder in publicly-traded company. **Men:** *Ascentage Pharma:* Current Employment, Current equity holder in publicly-traded company. **Wang:** *Ascentage Pharma:* Current Employment, Current equity holder in publicly-traded company. **Ahmad:** *Ascentage Pharma:* Current Employment, Current equity holder in publicly-traded company. **Yang:** *Ascentage Pharma:* Current Employment, Current equity holder in publicly-traded company, Membership on an entity's Board of Directors or advisory committees, Other: Leadership, Patents & Royalties. **Zhai:** *Ascentage Pharma:* Current Employment, Current equity holder in publicly-traded company, Other: Leadership (CMO).

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Table 1. Preliminary Efficacy Analysis

ORR, % (no. of efficacy evaluable pts)	Alrizomadlin	Alrizomadlin + AZA
Relapsed or refractory AML	25 (4/16)	33.3 (1/3)
– sAML transformation from MDS	50 (3/6)	0 (0/0)
Relapsed/progressed MDS*	50 (2/4)	100 (3/3)
Exposure to venetoclax + HMA	10 (1/10)	50 (2/4)

*All these MDS pts were exposed to cycles of HMA. AML, acute myeloid leukemia; HMA, hypomethylating agents; MDS, myelodysplastic syndrome; ORR, overall response rate; sAML, secondary AML.

Figure 1. Safety Analysis

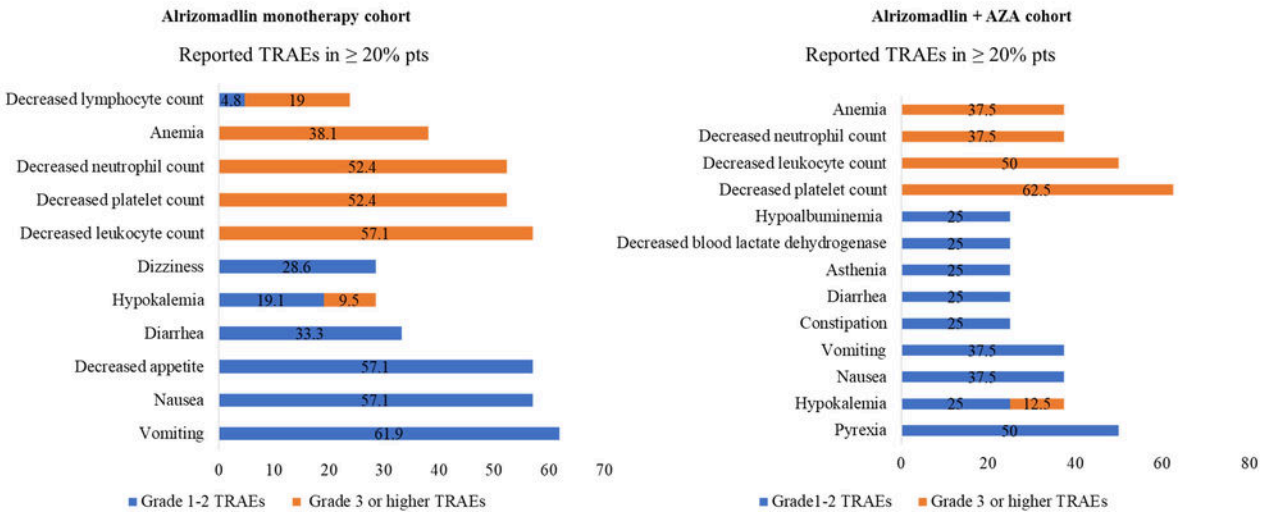

Figure 1

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