450 TRIAL IN PROGRESS: A PHASE 1B STUDY OF ALRIZOMADLIN, ALONE OR PLUS 5-AZACITIDINE OR CYTARABINE, IN PTS WITH RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA AND RELAPSED HIGHER-RISK MYELODYSPLASTIC SYNDROME

[1]Yifan Zhai, [2]Jianxiang Wang*. [1]*Ascentage Pharma, Rockville, MD, USA*; [2]*Blood Diseases Hospital Chinese Academy, Tianjin, China*

Background Patients with relapsed/refractory acute myeloid leukemia (R/R AML) and higher-risk myelodysplastic syndrome (MDS) have fewer approved effective treatment options, especially in the absence of a targetable mutation. Certain treatment-resistant cancers overexpress mouse double minute 2 homolog (MDM2) which is a negative regulator of tumor suppressor p53. Alrizomadlin (APG-115) is a novel, orally active, potent, small-molecule selective inhibitor that destabilizes the p53-MDM2 complex and activates p53-mediated apoptosis in tumor cells with wild-type TP53 and/or MDM2 amplification. Alrizomadlin can also augment MDM2-modulated signal transducer and activator of transcription 5 (STAT5) stability, which in turn can increase survival and function of tumor-infiltrating $CD8^+$ T cells. There is preclinical evidence of antitumor synergy when alrizomadlin is combined with immune checkpoint inhibitors. Through these pathways, alrizomadlin functions as an immunomodulator and may be complementary to other therapies in restoring antitumor activity.

Methods This open-label trial in Chinese patients is evaluating the safety and tolerability of oral alrizomadlin in adults with histologically confirmed R/R AML (according to WHO classification); relapsed/progressed, high- (or very high-) risk MDS according to IPSS-R stratification; an ECOG performance status of 0 to 1; and leukocytes $< 50 \times 109$/L. Excluded are patients with acute promyelocytic leukemia, a recent history of hematopoietic stem cell transplantation, uncontrolled cardiovascular diseases and certain active infections, and/or recent anticancer therapies. Alrizomadlin is administered orally once daily (QD) from Days 1 to 7 every 28 days. Part 1 is a standard 3 + 3 dose-escalation to determine the dose-limiting toxicity (DLT), maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D) of alrizomadlin. Part 2 will determine DLT, MTD, and RP2D of alrizomadlin combined with either 5-azacitidine (Arm A; 75 mg/m2 subcutaneously QD on Days 1–7 of a 28-day cycle) or cytarabine (Arm B; 1 g/m2 IV QD on Days 3–7 of a 28-day cycle). Part 3 is a dose-expansion of the alrizomadlin combination regimens at RP2D. The primary outcome measure comprises DLTs, which are defined as clinically significant drug-related adverse events during Cycle 1 (graded by NCI CTCAE v5). Secondary endpoints include (1) overall response rate (complete response [CR] + CR with incomplete hematologic recovery + partial response) measured up to 6 cycles for 1 month after the last dose and (2) overall survival measured up to 6 months after the last treatment dose. As of July 16, 2021, 7 patients have been enrolled. Internal study identifier APG115AC101. Clinical trial registration: NCT04275518.

Trial Registration Clinical trial registration: NCT04275518

http://dx.doi.org/10.1136/jitc-2021-SITC2021.450