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POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Development of Oral Azacitidine with Cedazuridine for Myelodysplastic Syndrome (MDS) and Myeloproliferative Neoplasms (MPN) Including CMML (Chronic Myelomonocytic Leukemia) By Targeting Pharmacokinetic AUC Equivalence Vs Subcutaneous Azacitidine

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Introduction/ Background:
Hypomethylating agents (HMAs) such as azacitidine (AZA) and decitabine (DEC) are FDA-approved for patients with MDS/CMML and acute myeloid leukemia (AML). Treatment is generally administered parenterally as a daily injection or infusion over 5-7 days per four-week cycle. The oral fixed-dose combination of decitabine with cedazuridine, ASTX727, was approved by regulators in the USA and Canada for patients with MDS and CMML based upon the demonstration of biologically equivalent pharmacokinetics (PK) area under the curve (AUC) vs IV decitabine. ASTX030 is a combination of AZA and cedazuridine (CED), a cytidine deaminase inhibitor (CDAi), which enables oral AZA to achieve systemic AUC similar to that of parenteral (subcutaneous) AZA. Development and approval of an oral AZA providing equivalent PK exposure to the parenteral therapy has the potential to markedly reduce the treatment burden associated with parenteral treatment. This Phase I trial is designed to determine the dose combination for oral AZA plus CED to replicate SC AZA AUC exposures in subjects with MDS and MDS/MPN, including CMML.

Methods:
Adult patients with confirmed MDS, CMML, and other MDS/MPN or AML who are candidates to receive benefit from single agent AZA were enrolled in this open label Phase 1 trial. In addition to assessing safety and efficacy of each combination, the primary PK endpoint was to achieve oral AZA PK AUC $_{0\text{-}24}$ equivalence versus subcutaneous AZA (at the approved dose of 75 mg/m ^{2} over the span of 7 days). In the first cycle, patients received oral AZA alone on Day -3, followed by SC AZA at 75 mg/m ^{2} on Day 1. Subsequently, oral ASTX030 (combination of AZA with CED) was given at varying dose combinations of AZA and CED for each cohort. After cycle 1, patients received oral ASTX030 on Days 1-7 for each 28-day cycle. Dose levels for cohorts in escalation were determined by the data safety and review committee based on safety and PK results. Pharmacodynamic (PD) impact was assessed by changes in *LINE-1* DNA methylation in peripheral blood cells. Clinical response assessments were based upon International Working Group (IWG) 2006 criteria for MDS patients and IWG 2015 criteria for MDS/MPN and CMML patients.

Results:
As of 05 JUL 2023, 65 patients were treated across 8 different dose combinations, with ≥6 patients per cohort. The median age was 72 years old (range 26-87), 36.9% (n=24) were female, 6.2% (n=4), had previously received HMA treatment (unlimited). Of the enrolled patients, 69% (n=45) had MDS, 25%(n=16) had CMML, and 6% (n=4) had MDS/MPN (other). Evaluated dose levels for AZA ranged from 60-136mg and CED dose ranged from 20-100 mg. In cohorts 1-2, tablet formulation was tested first (AZA ranging 80-100mg with CED ranging 80-100mg). Starting with cohort 3, capsule formulation was introduced for AZA to optimize the interaction effect of CDA inhibition by CED. In both tablet and capsule formulation, grade ≥3 AE's

(regardless of causality) were observed in 75.9% of patients. The most common Grade ≥3 AE's regardless of relation to drug were leukopenia (25%), thrombocytopenia (20%), and anemia (20%). Gastrointestinal toxicity were similar (for example, nausea 70% ASTX030 vs 71% SC AZA) to those reported for SC AZA (VIDAZA USPI)). No dose limiting toxicity was observed in any of the cohorts. The CED dose of 20 mg resulted in ~100% bioavailability for AZA, suggesting inhibition in a linear range. *LINE-1* demethylation results were similar to those reported historically with SC AZA. Although a clinical response comparable to SC AZA was observed, the immature nature of the data requires continued analysis to yield results on treatment efficacy.

Conclusion:

ASTX030 successfully achieved the primary endpoint of PK equivalence versus SC AZA based on total cycle AUC. The dose combinations evaluated were well tolerated, and the safety profile similar to that of SC AZA, with no unique AE's. *LINE-1* demethylation and clinical response confirm the clinical activity of ASTX030. Phase 1B dose expansion for the ASTX030 study at the recommended dose combination of 144mg AZA with 20mg CED will begin soon to confirm PK equivalence for this dose level. An orally bioequivalent AZA based HMA offers significant opportunity for novel combinations and improved convenience for patients with high grade myeloid malignancy.

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