Abstract # 4395

Phase 2 Study of Oral Decitabine/Cedazuridine in Combination with Magrolimab for Previously Untreated Subjects with Intermediate to Very High-Risk Myelodysplastic Syndromes (MDS)

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BACKGROUND

Myelodysplastic syndrome (MDS) is a premalignant clonal hematopoietic disorder characterized by bone marrow (BM) failure due to the production of dysfunctional, dysplastic BM cells and primarily affects individuals over 60 years of age (Ma, Am J Med. 2012). Low and very low-risk subjects, as defined by the Revised International Prognostic Scoring System (IPSS-R; Greenberg et al., Blood 2012), are often treated with erythroid and myeloid growth factor support. The backbone of treatment in intermediate to high-risk patients has focused on hypomethylating agents (HMA) monotherapy. In higher risk disease, only HMAs have been shown to be beneficial and only hematopoietic stem cell transplantation in selected patients appears to be curative. Thus there is a clear unmet need, especially those patients with higher-risk MDS. Combination therapy with HMAs is currently being investigated to improve response rates, including use of an anti-CD47 monoclonal antibody (mAb).

The overexpression of the dominant antiphagocytic signal, CD47, represents an important checkpoint in evading programmed cell death (Chao et al., Nat Rev Cancer 2011). Increased CD47 expression has been found on the cell surface of a diverse array of human tumor types including leukemia and MDS (Majeti et al., Cell 2009). The anti-CD47 mAb magrolimab has demonstrated encouraging data in higher-risk MDS in combination with the HMA azacitidine (Sallman et al., ASCO 2022).

One of the difficulties with HMAs has been the requirement for parenteral therapy. Oral HMAs have recently been developed. However, the only oral HMA approved in MDS is oral decitabine/cedazuridine. Oral decitabine/cedazuridine is approved for use in patients with intermediate- to high-risk MDS, as well as in patients with chronic myelomonocytic leukemia (CMML), in the US, Canada, and Australia. The recent Phase 3 ASCERTAIN study in higher-risk MDS evaluating oral decitabine/cedazuridine had a complete response (CR) of 22% with an overall response of 62% and median overall survival of 31.7 months (Savona et al., ICMDS 2021). Oral decitabine/cedazuridine is the only orally available HMA providing AUC exposure equivalent to its parenteral form. Offering an oral HMA option may improve patient willingness to undergo treatment and compliance which in turn may improved outcomes (Zeidan et al., CLML 2022).

RATIONALE

- HMAs are approved for higher risk MDS (azacitidine, decitabine, oral decitabine/cedazuridine US package insert). Depending on the HMA used, parenteral therapy (subcutaneous or intravenous) is required 5-7 days each month, resulting in hospital or clinic visits on a chronic basis and represents a substantial burden for this primarily elderly population and their caregivers.
- Magrolimab has demonstrated encouraging preliminary data in the higher-risk MDS population in combination with azacitidine and this combination is currently being evaluated in a randomized Phase 3 study (ENHANCE, NCT04313881).
- **This phase 2 study examines the possibility of using an oral HMA (oral decitabine/cedazuridine) in combination with magrolimab to provide the benefits of combination therapy without the burden of significant parenteral therapy (4-6 additional clinic days each month).**

STUDY OBJECTIVES

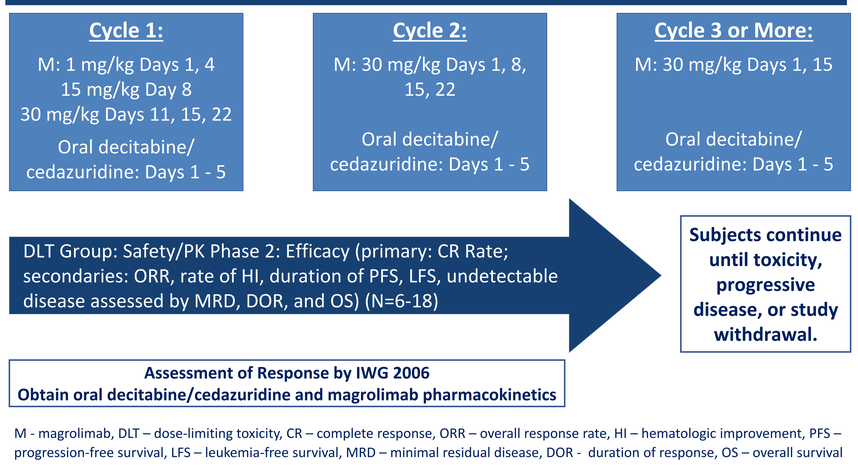
Primary Objective

- To evaluate preliminary safety and efficacy of oral decitabine/cedazuridine in combination with magrolimab.

Secondary Objectives

- To evaluate the PK profile of oral decitabine/cedazuridine and magrolimab.
- To evaluate other endpoints of clinical efficacy of oral decitabine/cedazuridine and magrolimab.
- To evaluate efficacy and safety in prespecified subgroups (eg, IPSS-M, p53 status).

STUDY SCHEMA



M - magrolimab, DLT – dose-limiting toxicity, CR – complete response, ORR – overall response rate, HI – hematologic improvement, PFS – progression-free survival, LFS – leukemia-free survival, MRD – minimal residual disease, DOR - duration of response, OS – overall survival

STUDY DESIGN

- ASTX727-10 is a phase 2, international, single-arm, open-label study investigating the safety and efficacy of combination oral decitabine/cedazuridine and magrolimab treatment in intermediate to very high-risk MDS, based on the MDS International Prognostic Scoring System - Revised (IPSS-R).
- Tolerability of the combination regimen will be confirmed in the first 6-18 subjects. Dose and/or dosing decreases identified during this DLT assessment will be applied to the entire study.
- Approximately 100 subjects will be enrolled.
- Anticipated study opening is February 2023.
- Multicenter global study involving sites in North America, Asia Pacific and Europe

PATIENT POPULATION

Key Inclusion Criteria

- Men and women 18 years of age or older.
- Histological confirmation of untreated MDS per World Health Organization 2016 classification with <20% bone marrow blasts at screening
- Projected life expectancy of at least 3 months.
- Overall IPSS-R score ≥3.5 MDS (intermediate risk or higher).
- Eastern Cooperative Oncology Group (ECOG) performance status of ≤2.
- Hematopoietic stem cell transplant (HSCT) eligible without any pre-arranged HSCT on Cycle 1 Day 1, or HSCT ineligible.
- Hemoglobin ≥9 g/dL on the first day of drug administration, transfusions allowed.
- Red blood cell phenotyping or genotyping completed prior to study drug treatment.
- White blood cell count ≤20 × 103/μL prior to first dose and throughout study. Hydroxyurea can be used to achieve this goal prior to and during Cycles 1 and 2.

Key Exclusion Criteria

- Known history of human immunodeficiency virus (HIV) infection; or active hepatitis B virus (HBV) or active hepatitis C virus (HCV) infection.
- Significant medical diseases or conditions, as assessed by the investigators and sponsor, that would substantially increase the risk benefit ratio of participating in the study
- Abnormal biochemical indices including liver function testing and creatinine
- Known inherited or acquired bleeding disorders that have required medical intervention.
- Second malignancy, except treated basal cell or localized squamous skin carcinomas, localized prostate cancer, or other malignancies for which subjects are not on active anticancer therapies and have had no evidence of active malignancy for at least ≥1 year.
- Prior therapy for MDS with chemotherapy, allogenic SCT, or ≥1 full cycle of treatment with any HMA.
- History of therapy-related MDS, MDS evolving from a pre-existing myeloproliferative neoplasm (MPN), MDS/MPN including CMML, atypical chronic myeloid leukemia, juvenile myelomonocytic leukemia, and unclassifiable MDS/MPN.
- Prior anti-CD47 treatment.
- Previous SCT within 6 months before first dose administration, active graft versus-host disease, or requiring transplant-related immunosuppression.
- Clinical suspicion of active central nervous system (CNS) involvement by MDS.
- Cardiac disease (EF<50%, NYHA >3, unstable disease, prolonged QTc)

CONTACT INFORMATION

For more information on this study email: clinicaltrials@astx.com

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