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

Amer M. Zeidan1, Karen Mosher2, Sonia Souza3, Belo Mirakhuri2, Harold N. Kee2 and Jason A. Taylor2

1Yale University, New Haven, CT; 2Astex Pharmaceuticals, Inc., Pleasanton, CA

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 erythropoietin and myeloid growth factor support. The backbone of treatment in intermediate to high-risk patients has been based 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 (Majet al 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., ICMSD 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 improve outcomes (Zeidan et al., CMLL 2022).

METHODS

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 DESIGN

Cycle 1:

M: 1 mg/kg Days 1, 15
30 mg/kg Days 11, 15, 22
Oral decitabine/cedazuridine: Days 1 - 5

Cycle 2:

M: 30 mg/kg Days 1, 15
22
Oral decitabine/cedazuridine: Days 1 - 5

Cycle 3 or More:

M: 30 mg/kg Days 1, 15
22
Oral decitabine/cedazuridine: Days 1 - 5

Subjects continue until toxicity, progressive disease, or study withdrawal.

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 elevation.
• 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 21 full cycle of treatment with any HMA.
• History of therapy-related MDS, MDS evolving from a pre-existing myeloproliferative neoplasm (MPN), MDS/MPN including CMMML, 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