Phase II Study Evaluating Olutasidenib in Patients with *IDH1*-Mutated Clonal Cytopenia of Undetermined Significance or Lower-Risk Myelodysplastic Syndromes/Chronic Myelomonocytic Leukemia

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INTRODUCTION

CLONAL HEMATOPOIESIS

- Clonal hematopoiesis is a non-malignant clonal expansion of a hematopoietic stem cell population due to acquisition of somatic mutations with no morphologic evidence of a hematologic malignancy
  - Clonal cytopenia of undetermined significance (CCUS): presence of cytopenia (anemia: hemoglobin <12 g/dL in females or <13 g/dL in males; thrombocytopenia: platelet count <150 × 10^9 cells/L; neutropenia: absolute neutrophil count <1.8 × 10^9 cells/L)
  - Clonal hematopoiesis of indeterminate potential (CHIP): presence of somatic mutation with no cytopenia
- Observational studies have shown that CCUS with high-risk mutations are more likely to transform to acute myeloid leukemia (AML)
- One study demonstrates a progression rate of 100% in *IDH1/2*-mutated patients after 5 years of follow-up
- There are no FDA-approved strategies for the prevention of hematologic malignancies in CCUS

MYELODYSPLASTIC SYNDROMES AND CHRONIC MYELOMONOCYTIC LEUKEMIA

- *IDH1* mutations are detected in 3-4% of patients with myelodysplastic syndromes (MDS) or chronic myelomonocytic leukemia (CMML)
- Ivosidenib (IDH1 inhibitor) was approved for relapsed/refractory *IDH1*-mutated MDS
- No IDH1-directed therapies are approved in lower-risk, treatment-naïve MDS or CMML

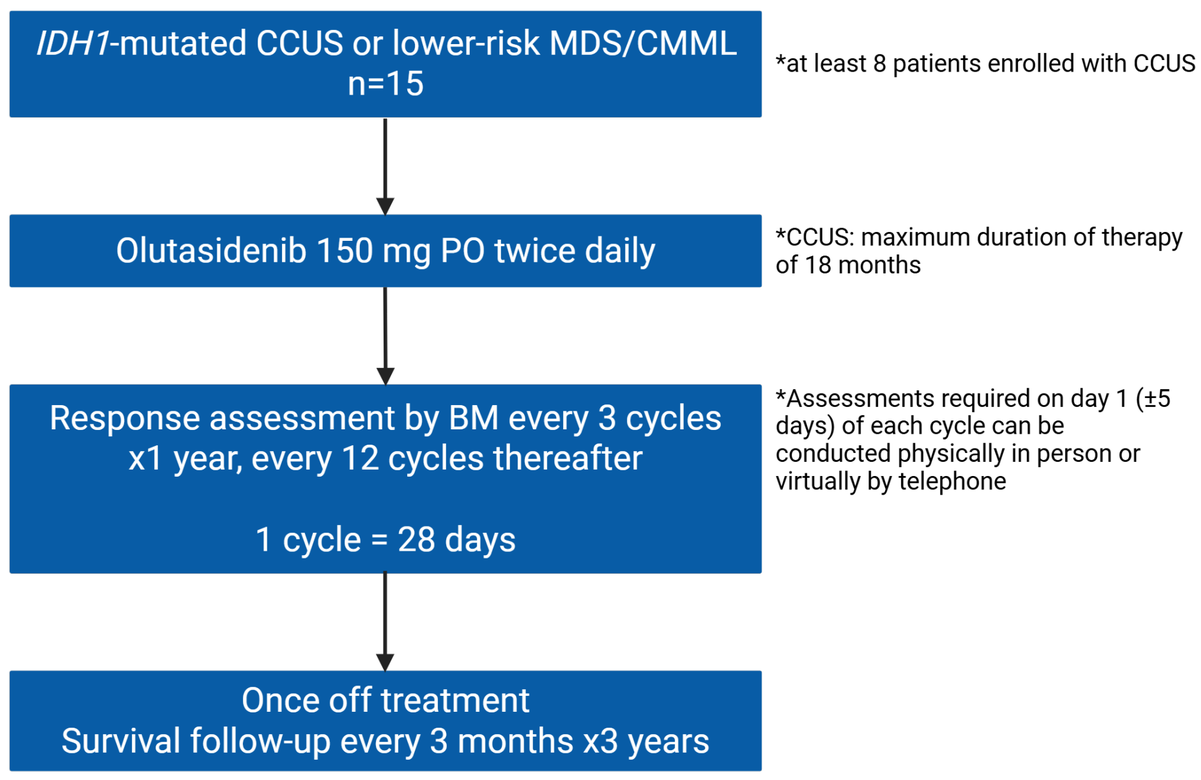
OLUTASIDENIB

- FDA-approved oral, highly selective, potent inhibitor of mutant IDH1
- Well-tolerated, non-cytotoxic, and effective with overall response rates in relapsed/refractory AML of 48% as monotherapy

HYPOTHESIS

Olutasidenib is effective in both improving hematologic parameters and decreasing the risk of progression to higher-risk MDS/CMML and AML in *IDH1*-mutated patients with CCUS or lower-risk MDS/CMML

TRIAL SCHEMA



ClinicalTrials.gov ID: NCT06566742

- Activated and enrollment began in December 2024 at MD Anderson
- Multicenter with plan to open across 5-7 center in the United States

ELIGIBILITY CRITERIA

INCLUSION CRITERIA

- CCUS or lower-risk MDS/CMML
  - CCUS: ANC < 1.8, Hgb < 13 in males or < 12 in females, platelets < 150
  - Lower-risk MDS/CMML by IPSS, IPSS-R, and IPSS-M
- *IDH1* mutation with VAF ≥ 0.02
- Age ≥ 18
- ECOG PS 0-2
- Acceptable liver and renal function
- Negative pregnancy test, use of contraception in fertile men/women, no ova or sperm donation
- Ability and willingness to sign informed consent

EXCLUSION CRITERIA

- Unable to swallow oral medications or with GI conditions
- Concurrent uncontrolled clinically significant medical condition
- Known active HBV or HCV
- Pregnant/nursing women, male or female who refuse to use contraception
- WBC > 25 (use of hydroxyurea okay with no washout)
- Inability or unwillingness to follow protocol procedures

OBJECTIVES/ENDPOINTS

OBJECTIVE	ENDPOINT
Primary	
To determine the response rate of olutasidenib monotherapy in patients with *IDH1*-mutated CCUS or lower-risk MDS/CMML	Hematologic improvement by IWG 2018
Secondary	
To evaluate the rates of transfusion independence	Absence of transfusions over a period of at least 8 weeks
To ascertain the safety and tolerability	CTCAE criteria
To determine survival and rates of transformation	Overall survival (OS), progression-free survival (PFS), duration of response (DOR), rates of leukemic transformation
To analyze reduction in *IDH1* clone size	*IDH1* clone size by VAF

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