ELSEVIER

Blood 142 (2023) 3253–3254

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Ivosidenib for Patients with Clonal Cytopenia of Undetermined Significance and Mutations in IDH1

Giulia Petrone, MDMBBS[1], *Eytan M. Stein, MD*[2], *Kelly L. Bolton, MD*[3]

[1] Washington University in St. Louis, Department of Medicine, Division of Hematology and Oncology, Saint Louis, MO
[2] Leukemia Service, Memorial Sloan Kettering Cancer Center, New York, NY
[3] Department of Medicine, Division of Oncology, Section of Stem Cell Biology, Washington University School of Medicine, Saint Louis, MO, Washington University In St Louis, St Louis, MO

Background

Myeloid neoplasms (MN), including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), are hematologic malignancies that are highly resistant to therapy and confer a poor prognosis. Recent studies have revealed that hematopoietic stem cells and progenitor cells carrying preleukemic mutations, defined as clonal hematopoiesis (CH), are the cells of origin in MN. CH can occur many years before the diagnosis of MN. Multiple mutations, mutations with a high variant allele frequency (VAF), and mutations in *TP53*, spliceosome genes, and isocitrate dehydrogenase 1/2 (*IDH1/2)* have been identified as high-risk features for CH progression to MN. Individuals with cytopenias who harbor acquired mutations in their blood yet do not meet criteria for hematologic malignancy, an entity called clonal cytopenia of undetermined significance (CCUS), have an even higher risk of developing MN (estimated at 95% over 10 years of follow-up). Thus, despite being almost inevitably destined for progression to malignancy, there are no established preventative therapies for patients with CCUS.

The *IDH1* inhibitor ivosidenib has been extensively evaluated in clinical studies and has been shown to effectively inhibit the gain-of-function activity of the mutated protein. Clinical data has shown that ivosidenib is safe and well-tolerated with excellent response rates even in patients with relapsed or refractory AML. Individuals with lower co-mutational burden are more likely to have a clinical response and achieve molecular remission with ivosidenib. Since CCUS is characterized by a lower mutation burden compared to AML or MDS, we hypothesize that the use of ivosidenib in *IDH1*-mutant CCUS will result in a higher and more prolonged clinical response.

Study Design and Methods

NCT05030441 is a decentralized open label, multicenter pilot study exploring the efficacy of ivosidenib in patients with *IDH1*-mutant CCUS. The study is offered as a decentralized trial (DCT) where patients across the US can participate with study procedures occurring in the patient's home using telemedicine, mobile phlebotomy services and with local providers. By reducing barriers to trial participation, we expect that the DCT design will improve accessibility for this rare patient population. This represents an important step toward making personalized medicine available to a socio-economically diverse patient population and enables rare mutations to be studied at scale. Patients with CCUS harboring the *IDH1 R132* mutation are considered eligible if they do not have any concurrent active malignancy requiring treatment. Patients must have unexplained cytopenia lasting ≥6 months, defined as hemoglobin <10 g/dL, absolute neutrophil count $<1.8 \times 10^9$/L and platelets $<100 \times 10^9$/L, as well as adequate baseline organ function including renal and liver function, as per the National Institutes of Health Common Terminology Criteria for Adverse Events (NCI CTCAE) grading. Recruitment and data collection will be coordinated with local providers for patients that enroll remotely. A total of 15 patients will be accrued to receive ivosidenib 500 mg daily for up to 18 cycles. The primary endpoint is rate of improvement in hematologic parameters using specific cutoffs for erythroid, platelet and neutrophil responses based on the MDS response criteria. The study will be considered positive if at least 6 out of the 15 patients have a hematologic improvement. Secondary endpoints include change in mutant *IDH1* VAF, measured at baseline and every 3 cycles on peripheral blood samples, safety of ivosidenib, and AML/MDS-free survival which will be evaluated by descriptive statistics and Kaplan-Meier methodology. Enrollment opened in one US center and by decentralized structure in April 2022, with 3 patients accrued, and is expected to open in other US centers in 2023. If the study endpoints are met, our aim is to expand to a larger population with the goal of determining whether ivosidenib can prevent the development of hematologic malignancy in patients with *IDH1*-mutant CCUS.

Disclosures Stein: *Menarini:* Consultancy; *Genesis:* Consultancy; *Syndax:* Consultancy; *Servier:* Consultancy; *Abbvie:* Consultancy; *Neoleukin:* Consultancy; *Calithera:* Consultancy; *OnCusp:* Consultancy; *CTI Biopharma:* Consultancy; *Eisai:* Research Funding; *Novartis:* Consultancy; *Bristol Myers Squib:* Consultancy, Research Funding; *PinotBio:* Consultancy; *Agios:* Consultancy; *Janssen:* Consultancy; *Astellas:* Consultancy; *Syros:* Consultancy; *Daiichi:* Consultancy; *Aptose:* Consultancy; *Foghorn:* Consultancy; *Ono Pharma:* Consultancy; *Gilead:* Consultancy; *Genentech:* Consultancy; *Jazz:* Consultancy; *Blueprint:* Consultancy. **Bolton:** *GoodCell:* Membership on an entity's Board of Directors or advisory committees; *Servier:* Research Funding.

OffLabel Disclosure: Ivosidenib is an isocitrate dehydrogenase-1 (IDH1) inhibitor approved for the treatment of acute myeloid leukemia with a susceptible IDH1 mutation. Here we describe a trial in progress on the use of ivosidenib in patients with clonal cytopenia of undetermined significance (CCUS) harboring an IDH1 mutation. The purpose of the study is to determine whether treatment with ivosidenib can induce a hematologic response in patients with CCUS, thereby establishing that ivosidenib can modify the biology of the disease.

https://doi.org/10.1182/blood-2023-184977