

S167 PHASE II STUDY OF THE IDH2-INHIBITOR ENASIDENIB IN PATIENTS WITH HIGH-RISK IDH2-MUTATED MYELOYDYSPLASTIC SYNDROMES (MDS)

Author(s): Sangeetha Venugopal, Courtney DiNardo, Koichi Takahashi, Marina Konopleva, Sanam Loghavi, Gautam Borthakur, Amy DeZern, Lucia Masarova, Naval Daver, Nicholas J. Short, Yesid Alvarado, Farhad Ravandi, Guillermo Montalban-Bravo, Koji Sasaki, Ricardo Delumpa, Mikkael A. Sekeres, Bhumika Patel, Gail J. Roboz, Hagop Kantarjian, Guillermo Garcia-Manero

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Background:

Isocitrate dehydrogenase 2 (IDH2) mutations occur in 5% of patients (pts) with MDS. Enasidenib (ENA) is a selective oral inhibitor of the mutant IDH2 enzyme with single-agent activity in relapsed/refractory acute myeloid leukemia (AML).

Aims:

An open label phase II study designed to evaluate the efficacy and tolerability of ENA, as monotherapy or in combination with azacitidine (AZA) in pts with higher-risk IDH2-mutated MDS. (NCT03383575)

Methods:

Pts with higher-risk [Revised International Prognostic Scoring System risk > 3 or high molecular risk (HMR)] MDS/CMML or LB AML naïve to hypomethylating agents (HMA) received ENA100 mg orally daily for 28 d of each 28-d cycle + AZA 75 mg/m² IV or SC on d 1- 7 of each cycle (ENA+AZA), and pts with refractory or progressive MDS to prior HMA therapy received ENA alone (ENA), in 28-d cycles until unacceptable toxicity, relapse, transformation to AML, or progression. The primary endpoint was overall response rate (ORR) [complete remission (CR), marrow CR (mCR), partial remission (PR) and hematologic improvement (HI)]. Other endpoints include safety, and survival outcomes.

Results:

48 pts received ENA+AZA (n = 26) or ENA (n = 22). The median age was 73 yrs (range, 46-83). Most pts (72%) had HMR: ASXL1 (39%), and RUNX1 (17%). Median number Tx cycles was 4 (2–32) in the ENA+AZA, and 7 (1–23) in the ENA arm. Common Tx-related grade 3–4 AEs in the ENA+AZA arm were neutropenia (64%), thrombocytopenia (28%), and anemia (8%); these occurred in 10%, 0%, and 5%, in the ENA arm. Grade 3–4 infections occurred in 32% (ENA+AZA)

and 14% (ENA). IDH differentiation syndrome occurred in 3 pts (12%) in the ENA+AZA and 5 pts (24%) in the ENA arm. Two deaths occurred during the initial 60 d, both unrelated to study and due to COVID. In response-evaluable pts (n=46), ORR was 84% (n = 21/25; 24% CR + 8% PR+44% mCR+ 8% HI] in the treatment naïve ENA+AZA and 43% (n = 9/21; 24% CR+5%PR+5% mCR+10% HI) in the HMA failure ENA arm (Table). Most common reason for Tx discontinuation was disease progression (ENA+AZA 20%, ENA 33%).5 pts (20%) received HCT in the ENA+AZA and 1 (5%) in the ENA arm. 7 pts in the ENA+AZA and 5 in the ENA arm were ongoing at data cutoff (Dec 31, 2020). After a median follow up of 12.6 mo, median OS was 32.2 mo in the ENA+AZA and 21.3 mo in the ENA arm