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

Topic: 10. Myelodysplastic syndromes - Clinical

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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.

Response	Arm A (Untreated)	Arm B (HMA-failure)
Evaluable (N = 46)	ENA+AZA (N = 25)	ENA (N = 21)

Overall response rate (ORR), n (%)	**30 (68)**	**21 (84)**	**9 (43)**
Complete remission (CR)	11 (24)	6 (24)	5 (24)
Partial remission (PR)	3 (7)	2 (8)	1 (5)
Marrow CR (mCR)	12 (26)	11 (44)	1 (5)
Hematological improvement (HI) only	4 (9)	2 (8)	2 (10)
No response (NR), n (%)	**16 (35)**	**4 (16)**	**12 (57)**
Stable disease (SD)	14 (30)	4 (16)	10 (48)
Progressive disease (PD)	2 (4)	0 (0)	2 (10)

Summary/Conclusion: ENA is well tolerated and shows promising efficacy in *IDH2*-mutated higher risk MDS. Follow up and accrual is ongoing to better define duration and biomarkers of response.

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