ENASIDENIB PLUS AZACITIDINE SIGNIFICANTLY IMPROVES COMPLETE REMISSION AND OVERALL RESPONSE RATES VERSUS AZACITIDINE MONOTHERAPY IN MUTANT-IDH2 NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA (ND-AML)

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Background

Enasidenib (ENA) is an oral, small-molecule inhibitor of mutant IDH2 (mIDH2) proteins that reduces DNA methylation by suppressing the oncometabolite, 2-hydroxyglutarate (2-HG), thereby restoring function to α-ketoglutarate-dependent TET family enzymes and other substrates. Azacitidine (AZA) is a hypomethylating agent that reduces DNA methylation by inhibiting DNA methyltransferases. ENA and AZA each induce an overall response rate (ORR) of ~30% and a complete remission (CR) rate of ~20% in ND-AML. In vitro, combining ENA + AZA enhanced single-agent effects on releasing differentiation block. The randomized phase II portion of the open-label phase I/II AG-221-AML-005 study compared combination ENA + AZA vs. AZA monotherapy (AZA Only) in patients (pts) with mIDH2 ND-AML who were not eligible for intensive chemotherapy (NCT02677922).

Aims

Evaluate the efficacy, safety, and effects on 2-HG and mIDH2 VAF of combination ENA + AZA vs. AZA Only.

Methods

Pts aged ≥18 yrs with mIDH2 ND-AML, ECOG PS ≤2 and intermediate- or poor-risk cytogenetics were randomized 2:1 to ENA + AZA or AZA Only in 28-day (d) cycles. All pts received SC AZA 75 mg/m2/d x 7 d/cycle; pts randomized to ENA + AZA also received ENA 100 mg QD. The primary endpoint was ORR, ie, the proportion of pts achieving CR, CR with incomplete count recovery (CRi/CRp), partial remission (PR), or morphologic leukemia-free state (MLFS) (IWG 2003 criteria). Other endpoints included duration of response (DOR), overall survival (OS), event-free survival (EFS), and changes in 2-HG levels and mIDH2 VAF.

Results

In all, 101 pts were randomized to ENA + AZA (n=68) or AZA Only (n=33). Median age was 75 yrs (57-85); most pts (83%) had intermediate-risk cytogenetics. 21 pts in the ENA + AZA arm and 1 in the AZA Only arm were ongoing at data cutoff (Aug 2019). The most common reason for discontinuation was disease progression (ENA + AZA 31%, AZA Only 52%). Median number treatment (Tx) cycles was 10 (1-26) in the ENA + AZA arm and 6 (1-28) in the AZA Only arm. In the AZA Only arm, 7 pts (21%) received subsequent Tx with ENA after discontinuing AZA.

ORR and CR rate were significantly improved with ENA + AZA vs. AZA Only (Table), with a median DOR of 24.1 mo in the ENA + AZA arm vs. 12.1 mo in the AZA Only arm. Median OS was 22 mo in both arms (HR 0.99 [95%CI 0.52, 1.87]; P = 0.97). Median EFS was 17.2 and 10.8 mo in the ENA + AZA and AZA Only arms, respectively (HR 0.59 [95%CI 0.30, 1.17]; P = 0.13) (Figure). ENA + AZA was associated with significantly greater maximal changes from baseline (BL) in mIDH2 VAF (median -83.4% vs. -17.7% with AZA Only; P < 0.01) and 2-HG levels (median -97.8% vs. -54.3%; P < 0.01). No BL co-mutation predicted primary resistance.

Common Tx-related grade 3-4 adverse events in the ENA + AZA arm were thrombocytopenia (37%), neutropenia (35%), anemia (19%), and febrile neutropenia (15%); these occurred in 19%, 22%, 22%, and 16% of pts in the AZA Only arm. Grade 3-4 infections occurred in 18% of ENA + AZA pts and 31% of AZA Only pts. IDH differentiation syndrome was reported for 12 pts (18%) in the ENA + AZA arm.

Figure. Kaplan-Meier estimated event-free survival (EFS)

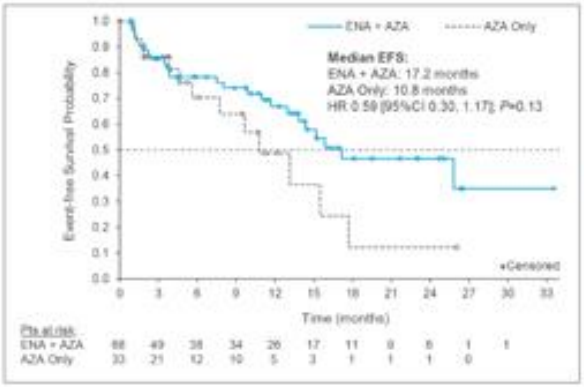

Table. Response

	ENA + AZA (n=68)	AZA Only (n=33)
ORR [CR, CRi/CRp, PR, MLFS], n (%) [95%CI]	48 (71) [58, 81]	14 (42) [26, 61]
P value	0.0064	
CR, n (%) [95%CI]	36 (53) [41, 65]	4 (12) [3, 28]
P value	0.0001	
CRi/CRp, n (%)	7 (10)	4 (12)
PR, n (%)	3 (4)	4 (12)
MLFS, n (%)	2 (3)	2 (6)
Stable disease, n (%)	13 (19)	13 (39)
Disease progression, n (%)	2 (3)	1 (3)
Not evaluable / Missing, n (%)	5 (7)	5 (15)
Duration of response, months, median [95%CI]	24.1 [11.1, NR]	12.1 [2.8, 14.6]

95%CI, 95% confidence interval; AZA, azacitidine; CR, complete remission; CRi/CRp, CR with incomplete hematologic or platelet recovery; ENA, enasidenib; MLFS, morphologic leukemia-free state; NR, not reached; ORR, overall response rate; PR, partial remission.

Conclusion

Combination ENA + AZA resulted in significantly improved response rates vs. AZA monotherapy and was generally well-tolerated in pts with mIDH2 ND-AML. ENA + AZA also led to deep reductions in 2-HG concentrations and mIDH2 VAF vs. AZA Only. Median OS in the AZA Only arm was longer than previous reports of AZA in pts with mIDH2 ND-AML. The impact of subsequent Tx on OS and EFS, and new translational data, will be presented at the meeting.

Session topic: 04. Acute myeloid leukemia - Clinical

Keyword(s): Acute myeloid leukemia, Azacitidine, Enasidenib