EP457 A PHASE 3 STUDY OF ENASIDENIB (ENA) VERSUS CONVENTIONAL CARE REGIMENS (CCR) IN OLDER PATIENTS WITH LATE-STAGE MUTANT-IDH2 (MIDH2) RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA (R/R AML)

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Background:

Prognosis is bleak for older patients (pts) with R/R AML, especially if multiple lines of treatment (Tx) have failed. Attaining response is more difficult after each Tx failure. IDH2 mutations occur in ~8-19% of pts with AML. ENA is an oral mIDH2 inhibitor shown to induce responses in pts with R/R AML

Aims:

Report clinical outcomes with ENA vs CCR from a phase 3 trial in older pts with late-stage mIDH2 R/R AML.

Methods:

This open-label trial enrolled pts aged ≥60 yrs with ECOG PS ≤2 and who received 2-3 prior AML Tx. Pts were first preselected to 1 of 4 CCR—azacitidine (AZA; 75 mg/m2 ×7d), intermediate-dose Ara-C (IDAC; 0.5–1.5 g/m2 ×3–6d), low-dose Ara-C (LDAC; 20 mg BID ×10d), or best supportive care (BSC) only—and then randomized 1:1 to ENA (100 mg QD) or preselected CCR in 28d cycles. Endpoints in the ITT cohort included overall survival (OS; primary), event-free survival (EFS), time to Tx failure (TTF), overall response rate (ORR), hematologic improvement (HI), and transfusion independence (TI). OS was also estimated in pts with mIDH2-R172 AML; in pts preselected for lower intensity Tx (AZA, LDAC, BSC) before randomization; and in efficacy-evaluable (E-E) pts (received ≥1 study drug dose and had ≥1 response evaluation on-Tx).

Results:

319 pts were randomized to ENA (n=158) or to CCR (n=161; AZA 69, IDAC 33, LDAC 37, BSC 22). Baseline (BL) characteristics were similar between Tx arms. Median age was 71 yrs, 21% of pts received ≥3 prior AML Tx, 40% had primary refractory AML, and 63% had ELN adverse-risk AML. In the ENA and CCR arms, respectively, median numbers of Tx cycles were 6 (range 1–44) and 2 (1–37), and Tx durations were 142d (3–1270) and 36d (1–1166). 20 CCR pts (12%) and 1 ENA pt did not receive any study Tx. 47 ENA pts (30%) and 69 CCR pts (43%) received subsequent AML Tx, including 19 CCR pts (12%) who received subsequent ENA.

Median OS (ITT) was not significantly different between ENA and CCR: 6.5 mo vs 6.2 mo (HR 0.86; P=0.23); 1-yr survival rates were 37.5% vs 26.1%. ENA also prolonged EFS and TTF vs CCR: median EFS was 4.9 vs 2.6 mo (P=0.008) and TTF was 4.9 vs 1.9 mo (P<0.0001). ORR was higher with ENA (40.5% vs 9.9%; P<0.0001), as were rates of CR (23.4% vs 3.7%; P<0.0001), HI (42% vs 11%; P<0.0001), and TI (Table). For pts preselected to lower-intensity Tx (ENA n=139; CCR n=128), median OS was 6.8 vs 6.2 mo with ENA vs CCR (HR 0.74; P=0.029). At BL, 88 pts had mIDH2-R172 AML; pts with the R172 variant had fewer BL co-mutations than mIDH2-R140 pts. In mIDH2-R172 pts, median OS was ~2-fold longer with ENA (n=43) vs CCR (n=45): 14.6 vs 7.8 mo (HR 0.59; P=0.039). In E-E pts (ENA 147; CCR 129), median OS was 6.8 vs 5.7 mo with ENA vs CCR (HR 0.77; P=0.047).

ENA safety was consistent with prior studies. IDH differentiation syndrome occurred in 14% of ENA pts, with median time to onset of 22d, and 17d to resolution. Tx-related G ≥3 hyperbilirubinemia occurred in 9% of pts.

	ENA N=158	CCR N=161
Overall survival (ITT), months, median [95%CI]	**6.5 [5.5, 9.5]**	**6.2 [4.6, 7.7]**
HR [95%CI]; log-rank *P*	0.86 [0.67, 1.10]; *P* = 0.23	
Overall survival (Efficacy Evaluable)	n=147	n=129
months, median [95%CI]	6.8 [5.7, 9.8]	5.7 [4.6, 7.6]
HR [95%CI]; log-rank *P*	0.77 [0.59, 1.00]; *P* = 0.047	
Event-free survival,* months, median [95%CI]	4.9 [3.7, 5.9]	2.6 [1.9, 4.4]
Time to treatment failure,† months, median [95%CI]	4.9 [4.0, 6.0]	1.9 [1.4, 2.5]
Overall response rate (ORR),‡ n (%)	64 (40.5)	16 (9.9)
CR rate, n (%)	37 (23.4)	6 (3.7)
Stable disease, n (%)	64 (40.5)	54 (33.5)
Disease progression, n (%)	13 (8.2)	29 (18.0)
Not evaluable,§ n (%)	17 (10.8)	62 (38.5)
Time to first response (ORR), days, median (range)	92 (24–337)	59 (29–177)
Duration of response (ORR),¶ months, median [95%CI]	7.3 [5.6, 11.1]	NE [2.5, NE]
RBC-Transfusion Independence (TI),‖ n/N (%)		
RBC-TD at BL, achieved TI on-study	33/104 (31.7)	9/97 (9.3)
RBC-TI at BL, retained TI on-study	32/53 (60.4)	7/44 (15.9)
Platelet-TI,‖ n/N (%)		
Platelet-TD at BL, achieved TI on-study	26/88 (29.5)	8/74 (10.8)
Platelet-TI at BL, retained TI on-study	48/69 (69.6)	22/67 (32.8)
Any Hematologic Improvement (HI),‖ n (%)	67 (42.4)	18 (11.2)
HI-Erythroid	21 (13.3)	9 (5.6)
HI-Platelet	31 (19.6)	7 (4.3)
HI-Neutrophil	57 (36.1)	13 (8.1)

*Time from randomization to relapse, PD, or death.
†Treatment discontinuation for any reason.
‡ORR includes CR, CRi/CRp, PR, and MLFS, per International Working Group (IWG) 2003 response criteria for AML.
§No postbaseline marrow collected (considered nonresponders; included in denominator for response assessments)
¶Date of first morphologic response to relapse, PD, or death.
‖Per IWG 2006 response criteria for MDS.
BL, baseline; CCR, conventional care regimens; CR, complete remission; CRi/CRp, CR with incomplete blood count/platelet recovery; ENA, enasidenib; HR, hazard ratio; MLFS, morphologic leukemia-free state; PR, partial remission; PD, progressive disease; RBC, red blood cell; TD, transfusion-dependent.

Conclusion:

Median OS was not significantly different between Tx arms in ITT analysis but results may be confounded by number of pts randomized but not treated, early Tx discontinuation, and subsequent Tx (including ENA)—which were all higher in the CCR arm. When the influence of no Tx or early Tx discontinuation was reduced (E-E analysis), OS was superior with ENA. ENA provided meaningful improvements in 1-yr survival, EFS, and morphologic response vs CCR, and ENA prolonged OS for pts

preselected to lower-intensity Tx and pts with mIDH2-R172 AML. HI and TI benefits also support ENA as appropriate oral outpatient Tx for pts with mIDH2 R/R AML.

Keyword(s): AML, Enasidenib, Mutation, Relapse