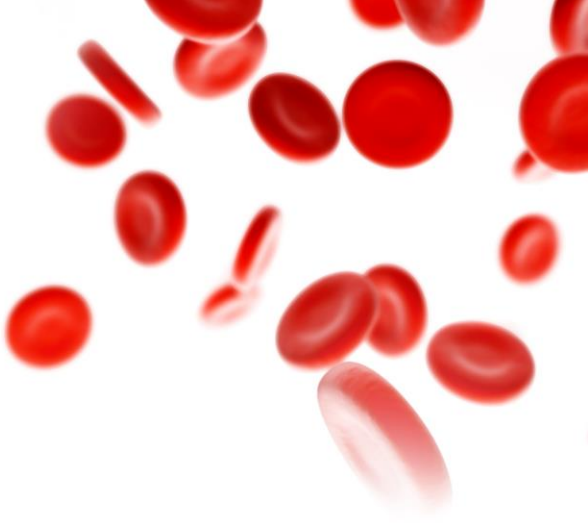

Enasidenib Plus Azacitidine Significantly Improves Complete Remission and Overall Response Rates vs AZA Monotherapy in Mutant-*IDH2* Newly Diagnosed Acute Myeloid Leukemia (ND-AML)

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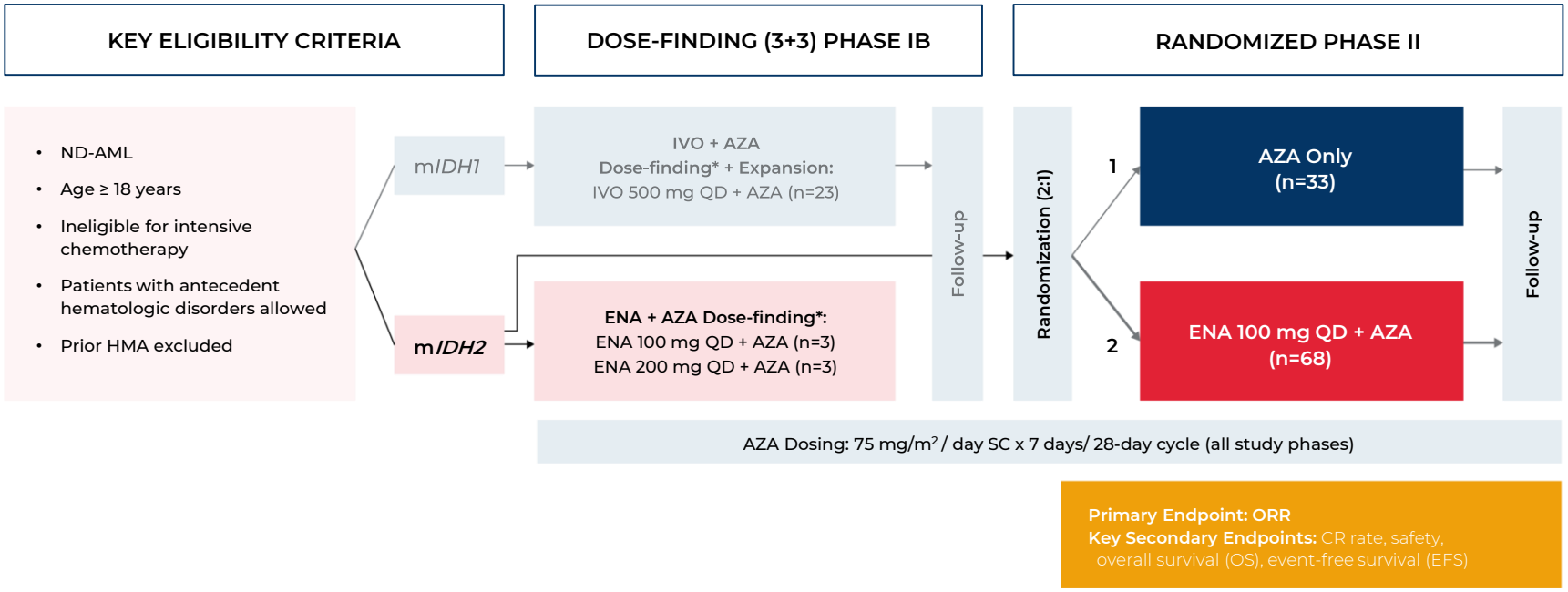
HEMA NEWS

AG221 -AML-005: Study design



*Dose finding for ENA or IVO; AZA dose remained constant.

AML, acute myeloid leukemia; AZA, azacitidine; CR, complete remission; EFS, event-free survival; ENA, enasidenib; HMA, hypomethylating agent; IVO, ivosidenib; m*IDH1* / m*IDH2*, mutant-*IDH1*/ mutant-*IDH2*; ND, newly diagnosed; ORR, overall response rate; OS, overall survival; SC, subcutaneous.

Response

- ORR and CR rate were both significantly higher with ENA + AZA *vs.* AZA Only

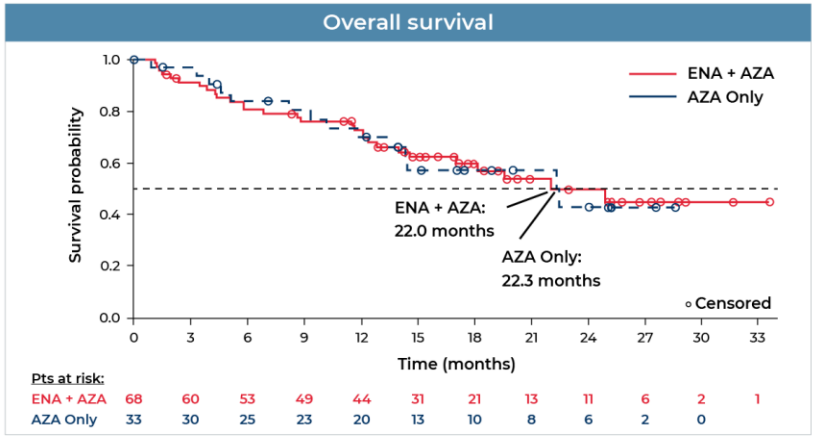
	ENA + AZA (n=68)		AZA Only (n=33)
Overall response (CR, CRi/CRp, PR, MLFS), n (%)	**48 (71)**		**14 (42)**
[ORR 95%CI]	**[58, 81]**		**[26, 61]**
***P* value**		**0.0064**	
CR, n (%)	36 (53)		4 (12)
[CR rate 95%CI]	[41, 65]		[3, 28]
P value		0.0001	
CRi/CRp, n (%)	7 (10)		4 (12)
PR, n (%)	3 (4)		4 (12)
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)
Time to first response, months, median (range)	1.9 (0.7-9.0)		2.0 (0.8-5.8)
Time to CR, months, median (range)	5.5 (0.7-19.5)		3.7 (3.0-4.1)
Duration of response, months, median [95%CI]	24.1 [11.1, NR]		12.1 [2.8, 14.6]

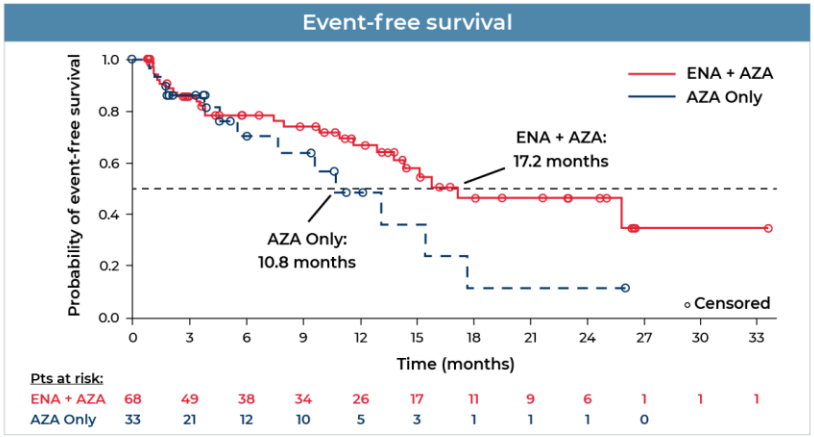
Data cutoff: August 19, 2019.

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.

Survival

- Median follow-up was 14 months in both treatment arms
- Median OS was 22.0 months in the ENA + AZA group and 22.3 months in the AZA Only group (HR 0.99 [95%CI 0.52, 1.87]; *P*=0.9686)
  - Among pts in the ENA + AZA arm who achieved CR, median OS was not reached and 1-year survival was over 90%
- Median EFS was 17.2 months with ENA + AZA, *vs.* 10.8 months with AZA Only (HR 0.59 [95%CI 0.30, 1.17]; *P*=0.1278)
- In the AZA Only arm, 8 patients (24%) received subsequent treatment with enasidenib monotherapy





Data cutoff: August 19, 2019
EFS: time from randomization to AML relapse, disease progression (IWG AML 2003 criteria), or death from any cause, whichever occured first.

Safety

- Median treatment exposure:
  - ENA + AZA: 10 cycles (range 1-26)
  - AZA Only: 6 cycles (range 1-28)
- Most common TEAEs with ENA + AZA and AZA Only: thrombocytopenia (62% and 44%), nausea (69% and 38%), anemia (53% and 44%), vomiting (49% and 47%)
- Common Tx-related grade 3-4 TEAEs in the ENA + AZA arm were cytopenias and IDH differentiation syndrome (IDH-DS)
  - Rates of Tx-related grade 3-4 infections were 18% in the ENA + AZA arm and 31% in the AZA-only arm
- 12 patients (18%) in the ENA + AZA arm experienced IDH-DS at a median of 28.5 days
  - Median time to IDH-DS resolution was 11.5 days
- 43% (n=29) of patients in the ENA + AZA arm and 44% (n=14) of patients in the AZA Only arm died

Grade 3-4 Tx-related TEAEs reported in ≥10% of patients in the ENA + AZA arm

	ENA + AZA (n=68)	AZA Only (n=32)
	n (%)	
Any grade 3 or 4 TEAE	50 (74)	20 (63)
Thrombocytopenia	25 (37)	6 (19)
Neutropenia	24 (35)	7 (22)
Anemia	13 (19)	7 (22)
Febrile neutropenia	10 (15)	5 (16)
IDH-DS	7 (10)	0

Deaths

	ENA + AZA (n=68)	AZA Only (n=32)
	n (%)	
Deaths, % (n)	43% (n=29)	44% (n=14)
Died while on Tx	22% (n=15)	6% (n=2)
Died after Tx discontinuation	21% (n=14)	38% (n=12)
60-day mortality rate, % (n	7% (n=5)	3% (n=1)

Data cutoff: August 19, 2019

AZA, azacitidine; ENA, enasidenib; IDH, isocitrate dehydrogenase; IDH-DS., IDH differentiation syndrome; TEAE, Tx-emergent adverse event; Tx, treatment.

Conclusions

- Combination ENA + AZA in patients with m*IDH2* ND-AML was associated with significantly improved ORR (71% *vs.* 42%; *P*=0.0064) and CR rates (53% *vs.* 12%; *P*=0.0001) *vs.* AZA monotherapy
- ENA + AZA led to deep reductions in 2-HG concentrations, indicative of on-target activity, and significantly greater maximal reductions in m*IDH2* VAF vs. AZA Only
- Median EFS was 17 months with ENA + AZA vs. 11 months with AZA Only; median OS was similar between Tx arms (22 months)
  - OS and EFS not powered for significance; OS confounded in AZA Only arm by subsequent ENA after discontinuation
  - For ENA + AZA patients who achieved CR, median OS was not reached and 1-year survival rate was >90%
- Responses were observed in patients with *FLT3*-ITD and RAS-pathway co-mutations, which have been associated with resistance to ENA monotherapy[1]
- ENA + AZA was generally well tolerated, with a safety profile similar to each as monotherapy[2-4]
  - During initial Tx cycles, patients should be monitored for infections and considered for prophylactic anti-infective Tx; corticosteroids should be initiated promptly upon suspicion of IDH-DS
- Combining targeted suppression of m*IDH2* oncogenic activity with ENA and broad anti-leukemic effects of AZA resulted in higher response rates than with either as monotherapy, and was well-tolerated in older patients with m*IDH2* AML

1. Amatangelo et al, *Blood*. 2017;130(6):732-41. 2. Dombret et al, *Blood*. 2015;126(3):291-9. 3. Stein et al, *Blood*. 2017;130(6):722-31. 4. Pollyea et al, *Leukemia*. 2019;33(11):2575-84.
AML, acute myeloid leukemia; CR, complete remission; ENA, enasidenib; IDH2, isocitrate dehydrogenase-2; IDH-DS, IDH differentiation syndrome; mIDH2, mutant-IDH2; ND, newly diagnosed; ORR, overall response rate; Tx, treatment.