Supplemental Table 1. Reasons for exclusion from the mITT analyses

Reason, n	**Enasidenib** (n=68 excluded from mITT)*	**CCR** (n=81 excluded from mITT)*
No retrospectively centrally confirmed diagnosis of AML	52	45
Violated inclusion/exclusion criteria	23	31
Did not receive randomized treatment	1	20
No post-randomization efficacy assessment	1	18

AML, acute myeloid leukemia; CCR, conventional care regimen; mITT, modified intention-to-treat.
*Patients may have met >1 criterion.

Supplemental Table 2. Baseline characteristics and prior AML treatment history in the modified intent-to-treat (mITT) population

Characteristic	Enasidenib (n=90)	CCR (n=80)	Total (N=170)
Age, years, median (range)	72 (60-84)	69 (60-84)	71 (60-84)
Age ≥80 years, n (%)	8 (9)	4 (5)	12 (7)
Sex, n (%)			
Male	53 (59)	50 (63)	103 (61)
Female	37 (41)	30 (38)	67 (39)
AML diagnosis, n (%)			
de novo	57 (63)	53 (66)	110 (65)
Secondary	33 (37)	27 (34)	60 (35)
Months since AML diagnosis, median	13.0	12.0	12.0
WHO AML classification, n (%)			
AML not otherwise specified	46 (51)	44 (55)	90 (53)
AML with myelodysplasia-related changes	24 (27)	22 (28)	46 (27)
AML with recurrent genetic abnormalities	16 (18)	12 (15)	28 (16)
Therapy related myeloid neoplasms	4 (4)	2 (3)	6 (4)
***IDH2* mutation type, n (%)**			
IDH2-R140	70 (78)	59 (74)	129 (76)
IDH2-R172	20 (22)	21 (26)	41 (24)
ECOG PS, n (%)			
0	22 (24)	14 (18)	36 (21)
1	54 (60)	50 (63)	104 (61)
2	14 (16)	16 (20)	30 (18)
ELN risk status, n (%)			
Favorable	8 (9)	5 (6)	13 (7)
Intermediate	13 (14)	12 (15)	25 (15)
Adverse	61 (68)	53 (66)	114 (67)

NE	8 (9)	10 (13)	18 (11)
Bone marrow blasts, %, median (range)	47 (6-99)	50 (5-98)	48 (5-99)
Hematologic parameters, median (range)			
ANC, 10^9/L	0.41 (0.0-15.4)	0.51 (0.0-8.1)	0.43 (0.0-15.4)
Hemoglobin, g/L	94 (57-136)	91 (54-132)	92 (54-136)
WBC, 10^9/L	2.5 (0.2-45)	2.8 (0.3-52)	2.6 (0.2-52)
Platelets, 10^9/L	37 (4-538)	35 (6-685)	37 (4-685)
Number of prior AML therapies,* n (%)			
2	70 (78)	61 (76)	131 (77)
3	29 (22)	19 (24)	39 (23)
Prior intensive chemotherapy, n (%)	67 (74)	60 (75)	127 (75)
Prior stem cell transplant, n (%)	8 (9)	8 (10)	16 (9)
Primary refractory AML,* n (%)	41 (46)	35 (44)	76 (45)
Prior relapse status, n (%)			
2 prior relapses	7 (8)	11 (14)	18 (11)
First remission ≤ 1 year	5 (6)	10 (13)	15 (9)

AML, acute myeloid leukemia; ANC, absolute neutrophil count; CCR, conventional care regimen; CR, complete remission; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; ELN, European LeukemiaNet; IQR, interquartile range; NE, not estimable; WBC, white blood cell; WHO, World Health Organization.

*Never attained CR, CRi, or CRp during prior AML-directed therapy.

Supplemental Table 3. Survival and response outcomes within CCR preselection subgroups

	Preselection: Azacitidine (n=142)		**Preselection: IDAC (n=52)**		**Preselection: LDAC (n=72)**		**Preselection: BSC only (n=53)**	
	Enasidenib (n=73)	**Azacitidine (n=69)**	**Enasidenib (n=19)**	**IDAC (n=33)**	**Enasidenib (n=35)**	**LDAC (n=37)**	**Enasidenib (n=31)**	**BSC only (n=22)**
OS, months, median (95% CI)	**10.2 (6.0-19.4)**	**7.7 (5.7-10.8)**	**6.2 (2.2-7.6]**	**6.6 (4.1-11.9)**	**5.9 (4.4-7.6)]**	**4.7 (3.0-7.0)**	**5.4 (2.8-12.5)**	**2.1 (1.3-8.5)**
ENA vs CCR: HR (95% CI)	0.97 (0.65-1.46)		NE		0.65 (0.38-1.11)		0.66 (0.3-1.23)	
1-year survival rate, %	46.3	31.9	15.8	29.0	34.3	21.0	34.6	14.3
EFS, months, median (95% CI)	**6.0 (3.9-9.3)**	**4.6 (2.6-6.2)**	**3.4 (2.0-7.4)**	**1.4 (0.8-11.0)**	**4.7 (3.0-5.9)**	**2.1 (1.1-4.7)**	**3.7 (1.5-5.8)**	**1.5 (0.4-1.9)**
ENA vs CCR: HR (95% CI)	0.80 (0.51-1.24)		NE		0.65 (0.36-1.18)		0.34 (0.15-0.77)	
ORR, n/N (%)	**38/73 (52)**	**12/69 (17)**	**7/19 (37)**	**2/33 (6)**	**9/35 (26)**	**2/37 (5)**	**10/31 (32)**	**0/22 (0)**
ENA vs CCR: OR (95% CI)	4.4 (2.0-9.6)		NE		5.3 (1.1-26.8)		NE	
Best response, n (%)								
CR	28 (38)	4 (6)	1 (5)	2 (6)	2 (6)	0	6 (19)	0
CRi/CRp	4 (5)	3 (4)	2 (11)	0	1 (3)	1 (3)	3 (10)	0
PR	4 (5)	0	0	0	3 (9)	0	0	0
MLFS	2 (3)	5 (7)	4 (21)	0	3 (9)	0	1 (3)	0
Stable disease	25 (34)	28 (41)	7 (37)	10 (30)	20 (57)	14 (38)	12 (39)	2 (9)
Disease progression	4 (5)	9 (13)	2 (11)	8 (24)	3 (9)	9 (24)	4 (13)	3 (14)
NE/not done*	6 (8)	20 (29)	3 (16)	13 (39)	3 (9)	12 (32)	3 (10)	17 (77)

	Preselection: Azacitidine (n=142)		Preselection: IDAC (n=52)		Preselection: LDAC (n=72)		Preselection: BSC only (n=53)	
	Enasidenib (n=73)	**Azacitidine (n=69)**	**Enasidenib (n=19)**	**IDAC (n=33)**	**Enasidenib (n=35)**	**LDAC (n=37)**	**Enasidenib (n=31)**	**BSC only (n=22)**
Any HI, n (%)	37 (51)	10 (14)	10 (53)	2 (6)	12 (34)	5 (14)	8 (26)	1 (5)
HI-erythroid	13 (18)	5 (7)	3 (16)	1 (3)	2 (6)	3 (8)	3 (10)	0
HI-neutrophil	33 (45)	6 (9)	7 (37)	2 (6)	10 (29)	4 (11)	7 (23)	1 (5)
HI-platelet	16 (22)	4 (6)	4 (21)	2 (6)	7 (20)	1 (3)	4 (13)	0

OS was estimated using Kaplan-Meier methods and compared between arms with HRs and 95% CIs from Cox proportional hazards regression models and *P* values from stratified log-rank tests. The 95% CIs for the 1-year OS differences were derived using Greenwood's variance estimate. EFS was estimated by Kaplan-Meier methods and compared between arms with HR and 95% CIs from a Cox proportional hazards regression model and *P* value from stratified log-rank test. ORR included CR, CRi/CRp, PR, and MLFS, per IWG 2003 response criteria for AML. Response rates were compared for enasidenib vs CCR by OR from a logistic regression model and *P* value from a Cochrane-Mantel-Haenszel test.

AML, acute myeloid leukemia; BSC, best supportive care; CCR, conventional care regimen; CI, confidence interval; CR, complete remission; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; EFS, event-free survival; ENA, enasidenib; HI, hematologic improvement; HR, hazard ratio; IDAC, intermediate-dose cytarabine; IWG, International Working Group; LDAC, low-dose cytarabine; MLFS, morphologic leukemia-free state; NE, not estimable; OR, odds ratio; ORR, overall response rate; OS, overall survival; PR, partial remission.

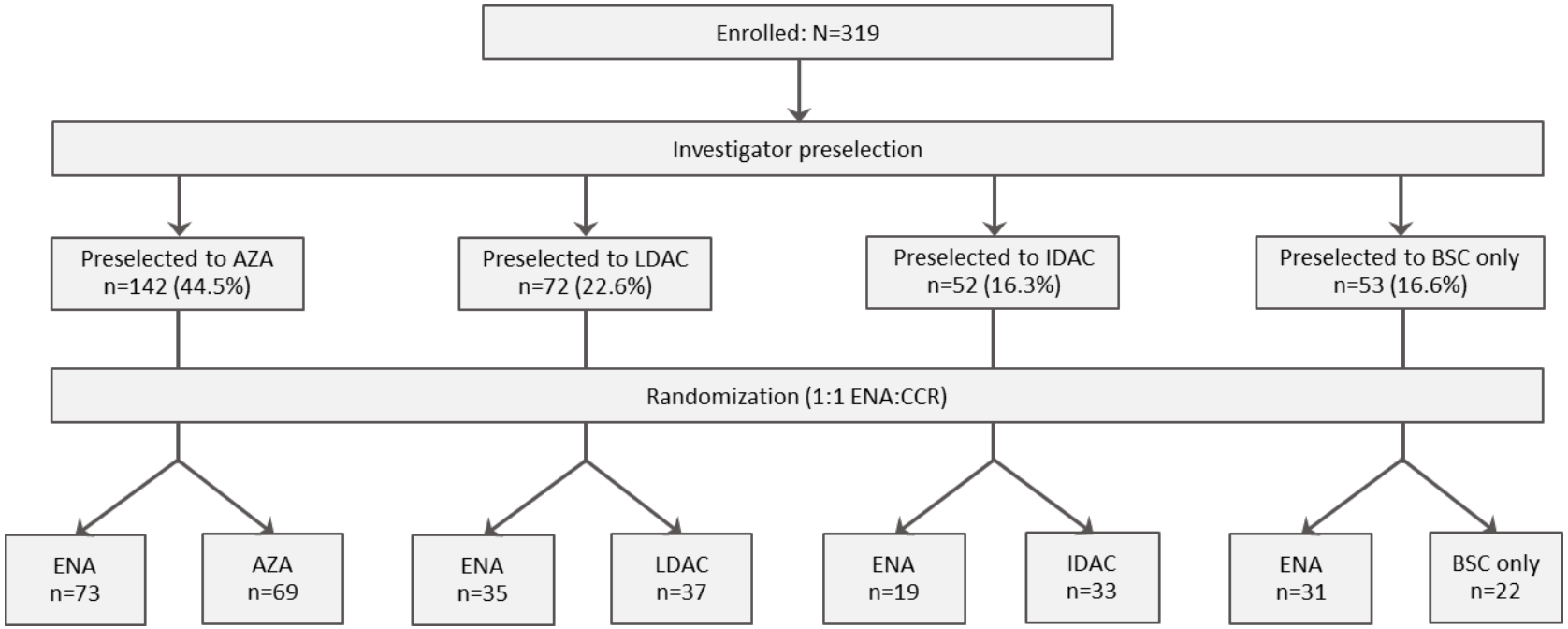
*No post-baseline bone marrow collected. Patients are considered non-responders and included in the denominator for response assessments.

Supplemental Table 4. Treatment-related grade ≥3 treatment-emergent adverse events in >2% of patients in either treatment arm and corresponding exposure-adjusted adverse event rates (EAERs)

	Enasidenib n=157 101.0 patient-years of treatment exposure		**CCR n=141 47.6 patient-years of treatment exposure**	
	Patients, n (%)	**Events, n (EAER*)**	**Patients, n (%)**	**Events, n (EAER*)**
Any grade ≥3 treatment-related TEAE	**74 (47.1)**	**175**	**49 (34.8)**	**151**
Thrombocytopenia	16 (10.2)	25 (24.7)	12 (8.5)	25 (52.5)
Blood bilirubin increased	13 (8.3)	13 (12.9)	0	0
Neutropenia	9 (5.7)	18 (17.8)	15 (10.6)	39 (81.9)
Differentiation syndrome	8 (5.1)	8 (7.9)	0	0
Anemia	7 (4.5)	13 [12.9]	7 (5.0)	9 (18.9)
Febrile neutropenia	4 (2.5)	7 (6.9)	17 (12.1)	21 (44.1)
Diarrhea	4 (2.5)	4 (4.0)	0	0
Pneumonia	1 (0.6)	1 (1.0)	6 (4.3)	6 (12.6)

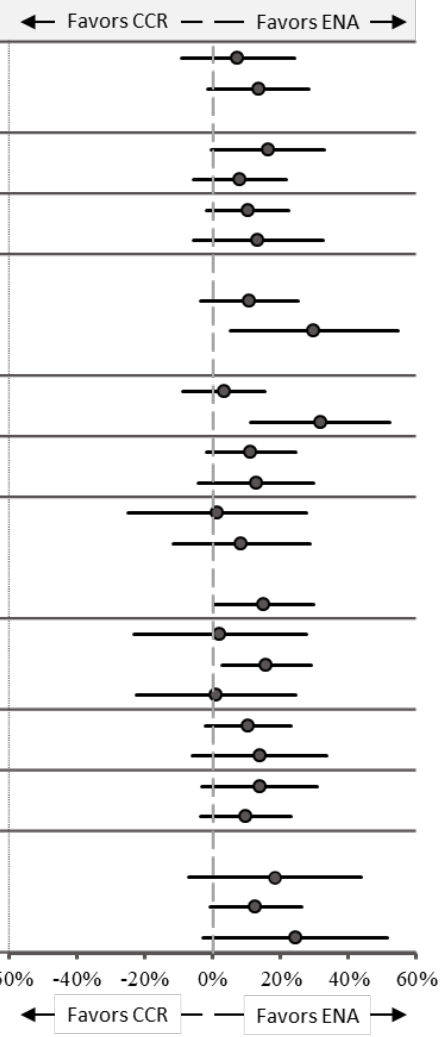
CCR, conventional care regimen; EAER, exposure-adjusted adverse event; TEAE, treatment-emergent adverse event.
*The EAER per 100 patient-years of exposure and is calculated as 100 × (n/TPY), where n is the total number of events in each group and TPY is total patient-years of exposure.

Supplemental Figure 1. Preselection and randomization



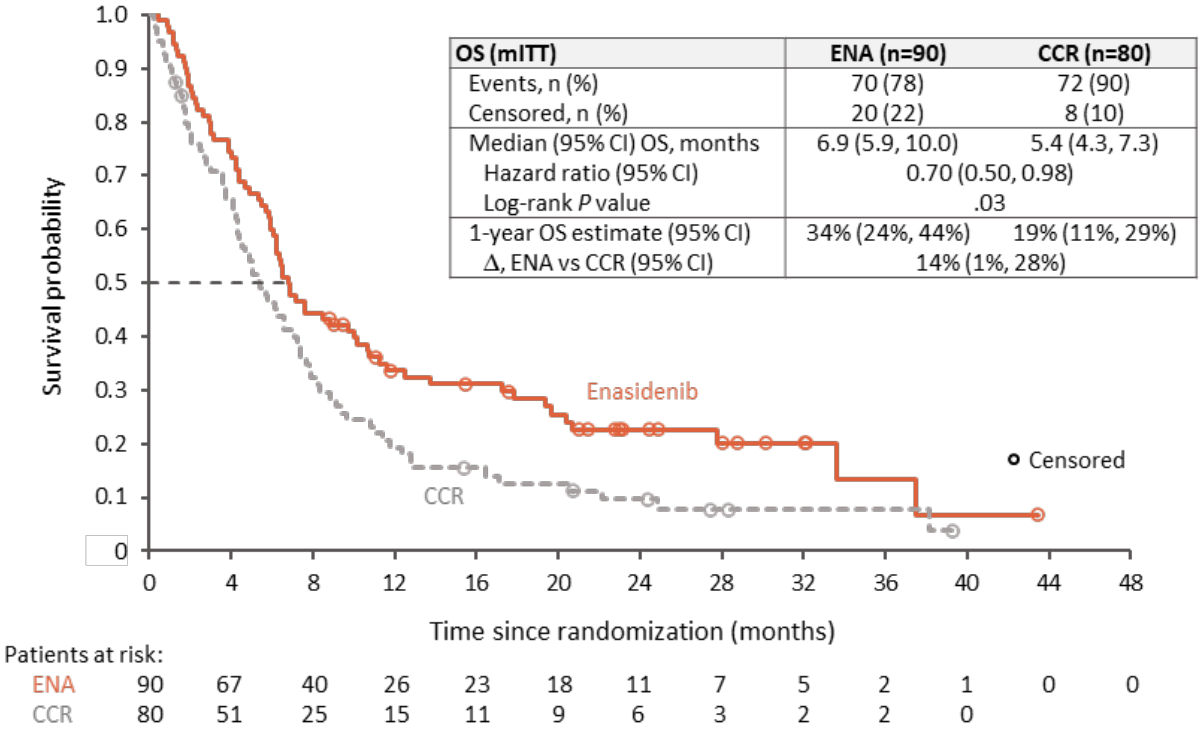
Supplemental Figure 2. 1-year survival rates in patient subgroups defined by baseline characteristics and prior AML treatment history

Subgroup	Patients, n		1-year OS rate, %		ENA vs CCR: 1-year OS difference, % (95% CI)
	ENA	CCR	ENA	CCR	
Age 60-69	61	72	37.5	30.1	+7.4 (-9.2 to +24.0)
Age 70-79	80	77	36.9	23.4	+13.6 (-1.4 to +28.5)
Age ≥ 80	17	12	39.7	19.0	NE
Female sex	67	65	40.7	24.4	+16.3 (-0.3 to +32.9)
Male sex	91	96	35.1	27.1	+7.9 (-5.7 to +21.6)
≤ 2 prior AML treatments	128	125	40.6	30.3	+10.4 (-1.8 to +22.5)
≥ 3 prior AML treatments	30	36	23.7	10.3	+13.4 (-5.7 to +32.6)
Better-risk cytogenetics	9	6	33.3	0	NE
Intermediate-risk cytogenetics	90	90	39.1	28.3	+10.7 (-3.7 to +25.2)
Poor-risk cytogenetics	22	27	40.9	11.1	+29.8 (+5.1 to +54.6)
Cytogenetic risk failed	4	1	50.0	NE	NE
IDH2-R140 mutation	115	114	28.5	25.1	+3.3 (-8.7 to +15.3)
IDH2-R172 mutation	43	45	61.7	30.0	+31.7 (+11.1 to +52.3)
de novo AML	106	115	40.9	29.8	+11.1 (-2.0 to +24.3)
Secondary AML	52	46	30.5	17.8	+12.8 (-4.4 to +29.9)
AML with recurrent genetic abnormalities	34	27	42.1	40.8	+1.4 (-24.9 to +27.6)
AML with myelodysplasia-related changes	41	41	33.7	25.2	+8.4 (-11.7 to +28.6)
Therapy-related myeloid neoplasms	4	5	50.0	20.0	NE
AML not otherwise specified	78	88	37.3	22.2	+15.1 (+0.6 to +29.6)
ECOG PS score 0	40	28	47.4	45.2	+2.1 (-23.4 to +27.7)
ECOG PS score 1	91	99	36.4	20.6	+15.8 (+2.6 to +28.9)
ECOG PS score 2	27	33	25.8	24.8	+1.1 (-22.4 to +24.5)
Prior intensive therapy for AML: Yes	117	117	37.4	27.1	+10.3 (-2.2 to +22.9)
Prior intensive therapy for AML: No	41	44	37.7	23.9	+13.8 (-6.0 to +33.6)
Primary refractory AML: Yes	65	64	43.5	29.7	+13.8 (-3.1 to +30.7)
Primary refractory AML: No	93	97	33.5	23.7	+9.7 (-3.7 to +23.1)
ELN favorable-risk	13	10	7.7	45.0	NE
ELN intermediate-risk	25	24	35.2	16.8	+18.4 (-7.0 to +43.8)
ELN adverse-risk	96	105	40.3	27.6	+12.7 (-0.8 to +26.1)
ENL risk NE	24	22	45.5	21.1	+24.3 (-2.9 to +51.6)



AML, acute myeloid leukemia; CCR, conventional care regimen; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ELN, European LeukemiaNet; ENA, enasidenib; NE, not estimatable; OS, overall survival.

Supplemental Figure 3. Median overall survival in the modified intention-to-treat (mITT) population



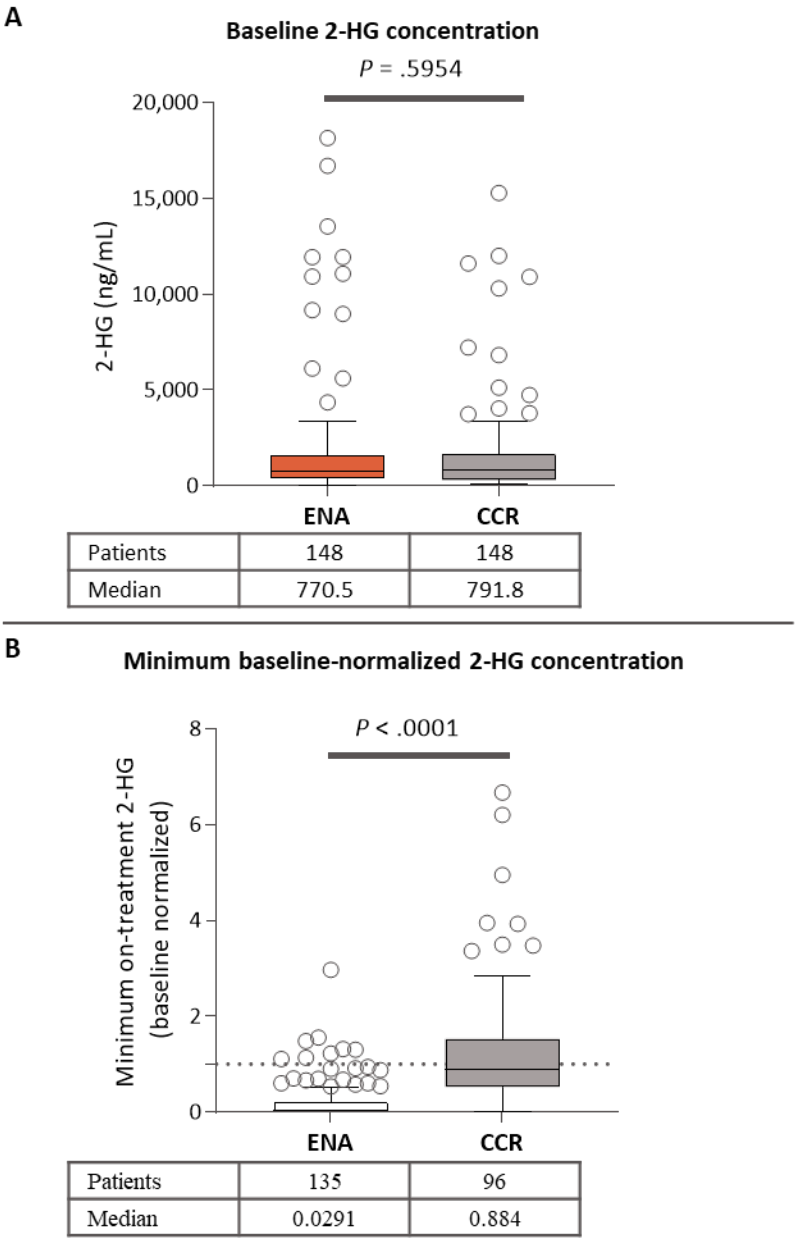
OS (mITT)	ENA (n=90)	CCR (n=80)
Events, n (%)	70 (78)	72 (90)
Censored, n (%)	20 (22)	8 (10)
Median (95% CI) OS, months	6.9 (5.9, 10.0)	5.4 (4.3, 7.3)
Hazard ratio (95% CI)	0.70 (0.50, 0.98)	
Log-rank *P* value	.03	
1-year OS estimate (95% CI)	34% (24%, 44%)	19% (11%, 29%)
Δ, ENA vs CCR (95% CI)	14% (1%, 28%)	

Patients at risk:

ENA	90	67	40	26	23	18	11	7	5	2	1	0	0
CCR	80	51	25	15	11	9	6	3	2	2	0		

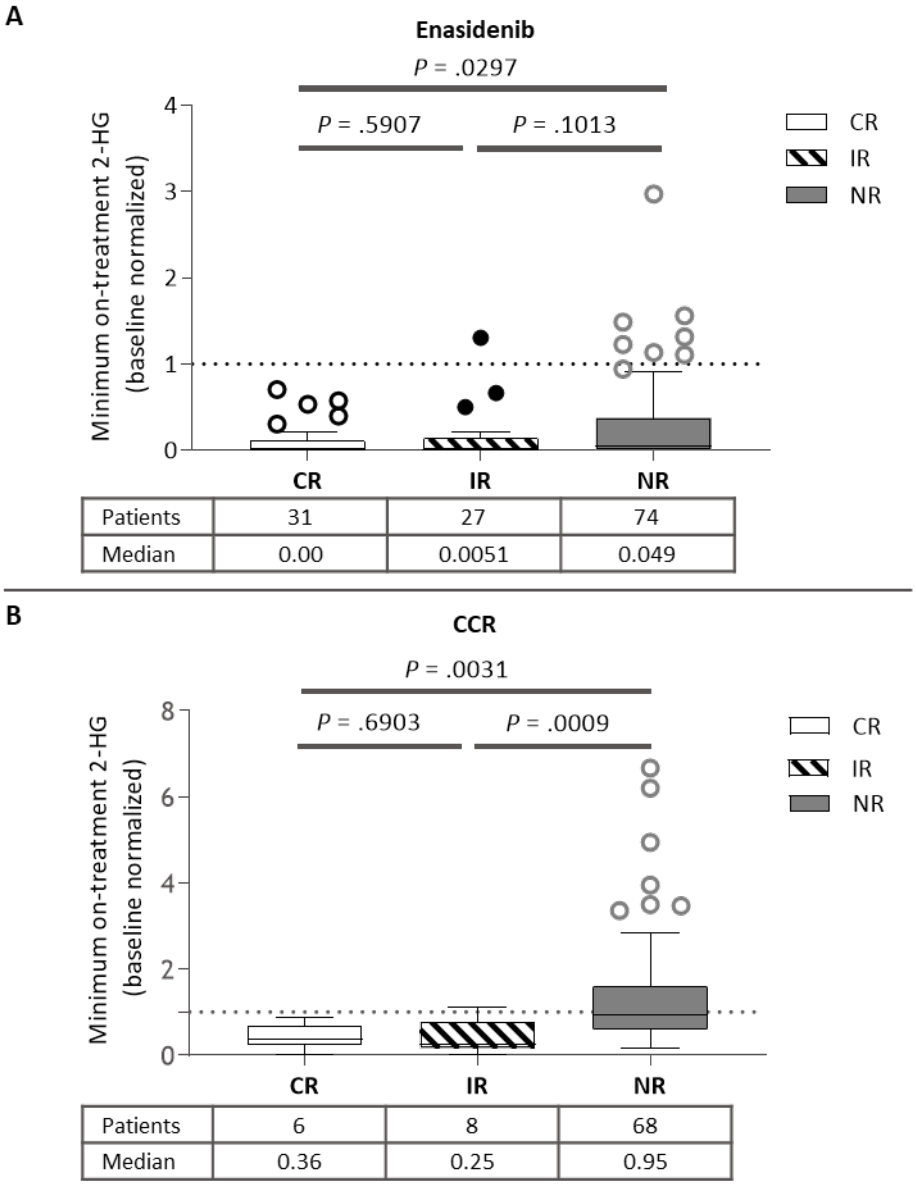
Δ, difference; CCR, conventional care regimens; CI, confidence interval; ENA, enasidenib; mITT, modified intention-to-treat; OS, overall survival.

Supplemental Figure 4. Baseline 2-HG concentration (A) and minimum baseline-normalized 2-HG concentrations on study (B)



Horizontal bars denote median; error bars denote Tukey's range; circles denote outliers.
2-HG, 2-hydroxyglutarate; CCR, conventional care regimen; ENA, enasidenib.

Supplemental Figure 5. Minimum baseline-normalized 2-HG concentrations on study by treatment arm and clinical response category



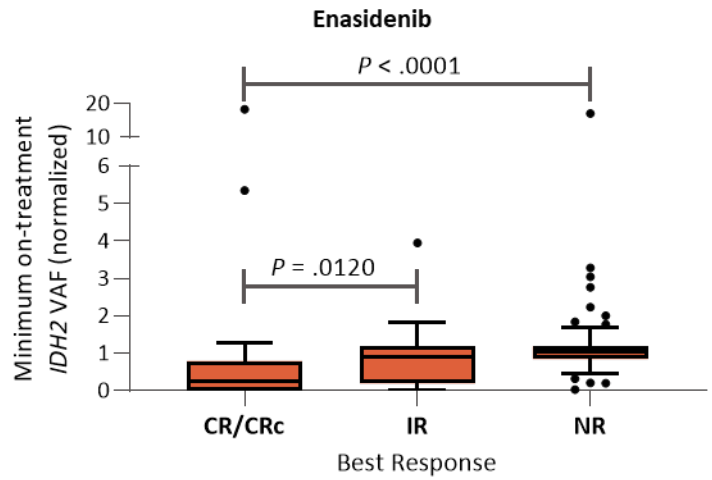
	CR	IR	NR
Patients	31	27	74
Median	0.00	0.0051	0.049

	CR	IR	NR
Patients	6	8	68
Median	0.36	0.25	0.95

Horizontal bars denote median 2-HG concentration at baseline. Error bars denote Tukey's range and circles denote outliers. The p-values were calculated using Mann-Whitney test. Incomplete response (IR) includes CR with incomplete blood count or platelet recovery (CRi/CRp), partial remission (PR), and morphologic leukemia-free state (MLFS).
CCR, conventional care regimen; CR, complete remission; IR, incomplete response; NR, no response.

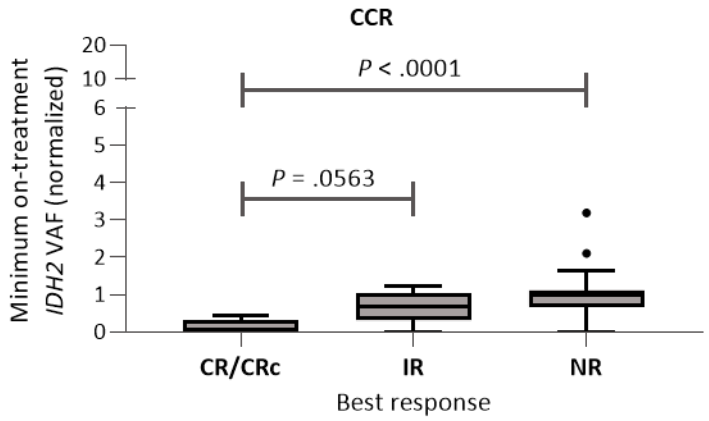
Supplemental Figure 6. Minimum baseline-normalized IDH2 VAF on study in the enasidenib (A) and CCR (B) treatment arms

A



Patients	30	24	64
Median (range) [95% CI]	0.26 (0, 18.3) [0.01, 0.72]	0.91 (0, 3.95) [0.21, 1.06]	1.03 (0.03, 17.0) [0.95, 1.09]

B



Patients	5	5	58
Median (range) [95% CI]	0 (0, 0.43) [0, 0.43]	0.69 (0, 1.22) [0, 1.22]	0.98 (0, 3.19) [0.91, 1.06]

Horizontal bars denote median baseline *IDH2* VAF. Error bars denote Tukey's range and circles denote outliers. The p-values were calculated using Mann-Whitney test. IR includes CR with incomplete blood count or platelet recovery (CRi/CRp), partial remission (PR), and morphologic leukemia-free state (MLFS). CCR, conventional care regimen; CR, complete remission; CRc, cytogenetic complete remission; IR, incomplete response; NR, no response; VAF, variant allele frequency.