SUPPLEMENTAL DATA

Supplemental Table 1. Baseline demographic and disease characteristics by *NPM1* mutational status at AML diagnosis

Characteristic	*NPM1*^{mut} (n = 137)	*NPM1*^{wt} (n = 332)	*P* value
Age, years, median	68	68	.245
Age category, n (%)			
55-64 years	42 (30.7)	92 (27.7)	
65-74 years	81 (59.1)	203 (61.1)	.804
≥75 years	14 (10.2)	37 (11.1)	
Sex, n (%)			
Male	60 (43.8)	183 (55.1)	.033
Female	77 (56.2)	149 (44.9)	
AML subtype, n (%)			
de novo	130 (94.9)	296 (89.2)	.054
Secondary	7 (5.1)	36 (10.8)	
NCCN cytogenetic risk at diagnosis, n (%)			
Intermediate	132 (96.4)	273 (82.2)	< .001
Poor	5 (3.6)	59 (17.8)	
***FLT3*-ITD^{+} or *FLT3*-TKD^{mut} at diagnosis**	45 (32.8)	21 (6.3)	< .001
Response after induction, n (%)			
CR	119 (86.9)	264 (79.5)	.067
CRi	18 (13.1)	68 (20.5)	
Received consolidation after induction, n (%)			
Yes	120 (87.6)	256 (77.1)	.011
No	17 (12.4)	76 (22.9)	
ECOG PS score, n (%)			
0	65 (47.4)	161 (48.5)	
1	64 (46.7)	142 (42.8)	.498
2-3	8 (5.8)	29 (8.7)	
MRD negative* at screening, n/N (%)	82/133 (61.7)	160/327 (48.9)	.014

*MRD determined at study entry by MFC using a "different-from-normal" method with a 0.1% positivity threshold.

AML, acute myeloid leukemia; CR, complete remission; CRi, CR with incomplete hematologic recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; *FLT3*, fms-like tyrosine kinase 3; ITD, internal tandem duplication; MFC, multiparameter flow cytometry; MRD, measurable residual disease; mut, mutation; NCCN, National Comprehensive Cancer Network; *NPM1*, nucleophosmin 1; TKD, tyrosine kinase domain; wt, wild type.

Supplemental Table 2. Baseline characteristics for patients with an *NPM1* mutation at AML diagnosis, by randomized treatment arm

Characteristic	Oral-AZA *NPM1*^{mut} (n = 66)	Placebo *NPM1*^{mut} (n = 71)	*P* value
Age, years, median	68	68	.799
Age category, n (%)			
55-64 years	20 (30.3)	22 (31.0)	
65-74 years	40 (60.6)	41 (57.7)	.900
≥75 years	6 (9.1)	8 (11.3)	
Sex, n (%)			
Male	26 (39.4)	34 (47.9)	.389
Female	40 (60.6)	37 (52.1)	
AML subtype, n (%)			
de novo	64 (97.0)	66 (93.0)	.443
Secondary	2 (3.0)	5 (7.0)	
NCCN cytogenetic risk at diagnosis, n (%)			
Intermediate	64 (97.0)	68 (95.8)	1.0
Poor	2 (3.0)	3 (4.2)	
***FLT3*-ITD^{+} or *FLT3*-TKD^{mut} at diagnosis**	20 (30.3)	25 (35.2)	.588
Response after induction, n (%)			
CR	57 (86.4)	62 (87.3)	1.0
CRi	9 (13.6)	9 (12.7)	
Received consolidation after induction, n (%)			
Yes	58 (87.9)	62 (87.3)	1.0
No	8 (12.1)	9 (12.7)	
ECOG PS score, n (%)			
0	35 (53.0)	30 (42.3)	
1	26 (39.4)	38 (53.5)	.228
2-3	5 (7.6)	3 (4.2)	
MRD negative* at screening, n/N (%)	39/66 (59.0)	42/67 (62.7)	.721

*MRD determined at study entry by MFC using a "different-from-normal" method with a 0.1% positivity threshold.

AML, acute myeloid leukemia; AZA, azacitidine; CR, complete remission; CRi, CR with incomplete hematologic recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; *FLT3*, fms-like tyrosine kinase 3; ITD, internal tandem duplication; MFC, multiparameter flow cytometry; MRD, measurable residual disease; mut, mutation; NCCN, National Comprehensive Cancer Network; *NPM1*, nucleophosmin 1; TKD, tyrosine kinase domain.

Supplemental Table 3. Impact of *NPM1* and *FLT3* mutational status at AML diagnosis on OS and RFS from randomization within randomized treatment arms

	Mutation	Wild type	OS, mutation vs wild type	RFS, mutation vs wild type
	n (%)		HR (95% CI); *P* value	
Oral-AZA, n = 236				
Gene				
NPM1	66 (28.0)	170 (72.0)	0.52 (0.36-0.75); *P* < .001	0.46 (0.31-0.66); *P* < .001
*FLT3**	30 (12.7)	206 (87.3)	0.96 (0.60-1.54); *P* = .871	0.62 (0.37-1.05); *P* = .071
FLT3-ITD	21 (8.9)	215 (91.1)	1.10 (0.65-1.88); *P* = .715	0.72 (0.39-1.32); *P* = .285
FLT3-TKD	11 (4.7)	225 (95.3)	0.84 (0.39-1.79); *P* = .648	0.69 (0.32-1.48); *P* = .329
Placebo, n = 233				
Gene				
NPM1	71 (30.5)	162 (69.5)	0.69 (0.49-0.97); *P* = .032	0.65 (0.47-0.91); *P* = .011
*FLT3**	36 (15.5)	197 (84.5)	1.25 (0.83-1.89); *P* = .280	1.07 (0.71-1.61); *P* = .76
FLT3-ITD	25 (10.7)	208 (89.3)	1.25 (0.78-2.02); *P* = .351	1.13 (0.70-1.82); *P* = .594
FLT3-TKD	13 (5.6)	220 (94.4)	1.03 (0.68-2.46); *P* = .422	1.01 (0.53-1.90); *P* = .996

*Includes *FLT3*-ITD and *FLT3*-TKD.

AZA, azacitidine; CI, confidence interval; *FLT3*, fms-like tyrosine kinase 3; HR, hazard ratio; ITD, internal tandem duplication; *NPM1*, nucleophosmin 1; OS, overall survival; RFS, relapse-free survival; TKD, tyrosine kinase domain.

Supplemental Table 4. Impact of Oral-AZA vs placebo on OS and RFS from time of randomization in patients with *NPM1* or *FLT3* mutations at AML diagnosis

	Oral-AZA, n	Placebo, n	OS, Oral-AZA vs placebo HR (95% CI); *P* value	RFS, Oral-AZA vs placebo HR (95% CI); *P* value
Gene mutation				
NPM1^{mut}, n = 137	66	71	0.63 (0.41-0.98); *P* = .038	0.55 (0.35-0.84); *P* = .005
FLT3^{mut}, n = 66*	30	36	0.63 (0.35-1.12); *P* = .114	0.51 (0.27-0.95); *P* = .032
FLT3-ITD^{+}, n = 46	21	25	0.68 (0.34-1.35); *P* = .270	0.54 (0.25-1.14); *P* = .099
FLT3-TKD^{mut}, n = 24	11	13	0.55 (0.21-1.46); *P* = .223	0.54 (0.20-1.44); *P* = .202

*4 patients had both *FLT3*-ITD and *FLT3*-TKD mutations.

AML, acute myeloid leukemia; AZA, azacitidine; CI, confidence interval; *FLT3*, fms-like tyrosine kinase 3; HR, hazard ratio; ITD, internal tandem duplication; mut, mutation; *NPM1*, nucleophosmin 1; OS, overall survival; RFS, relapse-free survival; TKD, tyrosine kinase domain.

Supplemental Table 5. Baseline demographic and disease characteristics by *FLT3* mutational status at AML diagnosis

Characteristic	*FLT3*^{mut} (n = 66)	*FLT3*^{wt} (n = 403)	*P* value
Age, median, years	67	69	.023
Age category, n (%)			
55-64 years	24 (36.4)	110 (27.3)	.395
65–74 years	37 (56.1)	247 (50.4)	
≥75 years	5 (7.6)	46 (11.4)	
Sex, n (%)			
Male	29 (43.9)	214 (53.1)	.185
Female	37 (56.1)	189 (46.9)	
AML subtype, n (%)			
de novo	63 (95.5)	363 (90.1)	.247
Secondary	3 (4.5)	40 (9.9)	
NCCN cytogenetic risk at diagnosis, n (%)			
Intermediate	63 (95.5)	342 (84.9)	.019
Poor	3 (4.5)	61 (15.1)	
***NPM1*^{mut} at diagnosis, n (%)**	45 (68.2)	92 (22.8)	< .001
Response after induction, n (%)			
CR	56 (84.8)	327 (81.1)	.607
CRi	10 (15.2)	76 (18.9)	
Received consolidation after induction, n (%)			
Yes	59 (89.4)	317 (78.7)	.046
No	7 (10.6)	86 (21.3)	
ECOG PS score, n (%)			
0	22 (33.3)	204 (50.6)	.027
1	36 (54.5)	170 (42.2)	
2-3	8 (12.1)	29 (7.2)	
MRD-negative at screening, n/N (%)	32/65 (49.2)	210/395 (53.2)	.593

AML, acute myeloid leukemia; CR, complete remission; CRi, CR with incomplete hematologic recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; *FLT3*, fms-like tyrosine kinase 3; MRD, measurable residual disease; mut, mutation; NCCN, National Comprehensive Cancer Network; wt, wild type.

Supplemental Table 6. Baseline characteristics for patients with a *FLT3* mutation at AML diagnosis, by randomized treatment arm

Characteristic	Oral-AZA *FLT3*^{mut} (n = 30)	Placebo *FLT3*^{mut} (n = 36)	*P* value
Age, years, median	67	67	.931
Age category, n (%)			
55-64 years	10 (33.3)	14 (38.9)	
65-74 years	17 (56.7)	20 (55.6)	.752
≥75 years	3 (10.0)	2 (5.6)	
Sex, n (%)			
Male	12 (40.0)	17 (47.2)	.623
Female	18 (60.0)	19 (52.8)	
AML subtype, n (%)			
de novo	30 (100.0)	33 (91.7)	.245
Secondary	0 (0.0)	3 (8.3)	
NCCN cytogenetic risk at diagnosis, n (%)			
Intermediate	29 (96.7)	34 (94.4)	1.0
Poor	1 (3.3)	2 (5.6)	
***NPM1*^{mut} at diagnosis**	20 (66.7)	25 (69.4)	1.0
Response after induction, n (%)			
CR	24 (80.0)	32 (88.9)	1.0
CRi	6 (20.0)	4 (11.1)	
Received consolidation after induction, n (%)			
Yes	27 (90.0)	32 (88.9)	1.0
No	3 (10.0)	4 (11.1)	
ECOG PS score, n (%)			
0	13 (43.3)	9 (25.0)	
1	14 (46.7)	22 (61.1)	.289
2-3	3 (10.0)	5 (13.9)	
MRD negative* at screening, n/N (%)	14/30 (46.7)	18/35 (51.4)	1.0

*MRD determined at study entry by MFC using a "different-from-normal" method with a 0.1% positivity threshold.

AML, acute myeloid leukemia; AZA, azacitidine; CR, complete remission; CRi, CR with incomplete hematologic recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; *FLT3*, fms-like tyrosine kinase 3; MFC, multiparameter flow cytometry; MRD, measurable residual disease; NCCN, National Comprehensive Cancer Network; *NPM1*, nucleophosmin 1.

Supplemental Figure 1. Treatment allocations and *NPM1*/*FLT3* mutational status at diagnosis in the biomarker cohort (n = 469). The biomarker cohort included patients with mutational data available from the time of AML diagnosis. *FLT3*^{mut} includes *FLT3*-ITD^{+} and *FLT3*-TKD^{mut}. AML, acute myeloid leukemia; AZA, azacitidine; *FLT3*, fms-like tyrosine kinase 3; ITD, internal tandem duplication; mut, mutation; *NPM1*, nucleophosmin 1; TKD, tyrosine kinase domain.