A phase I/II study of the combination of quizartinib with azacitidine or low-dose cytarabine for the treatment of patients with acute myeloid leukemia or myelodysplastic syndrome

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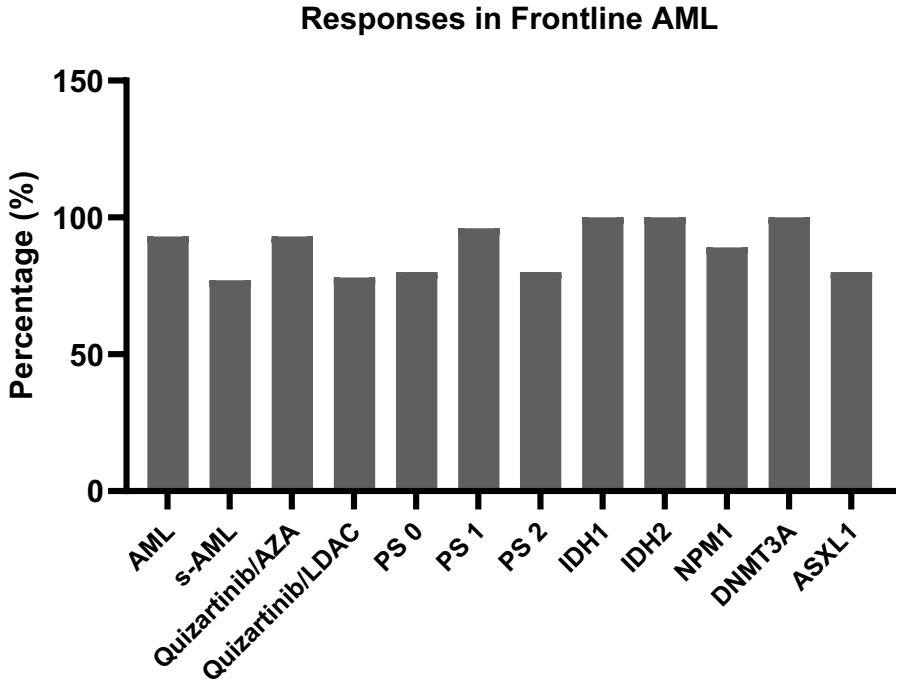
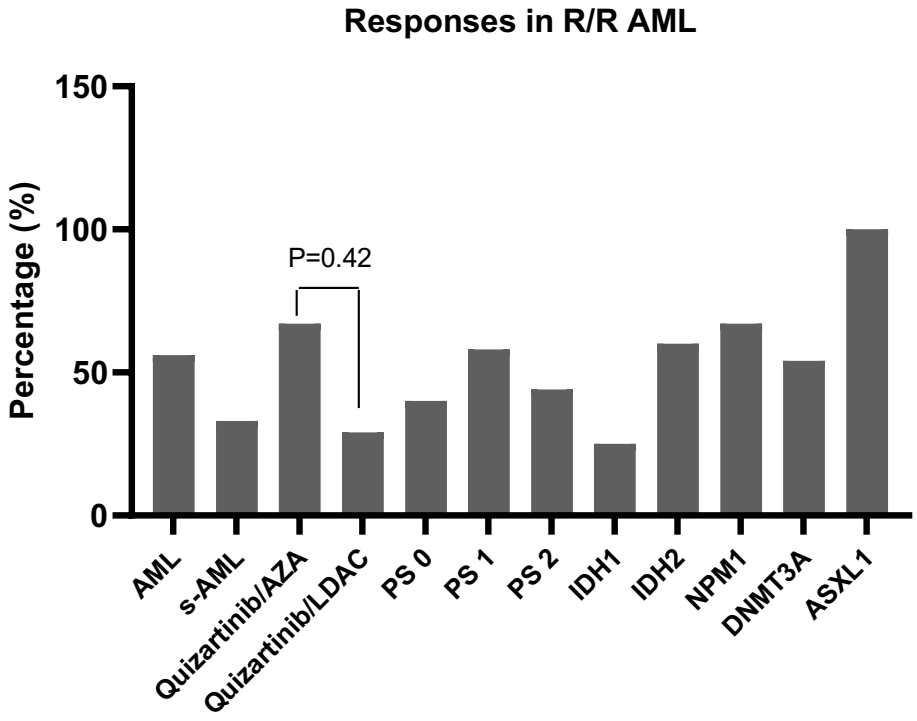
SUPPLEMENTARY:

Supplemental Figure 1: Association between composite response and covariates in frontline patients (n=34).



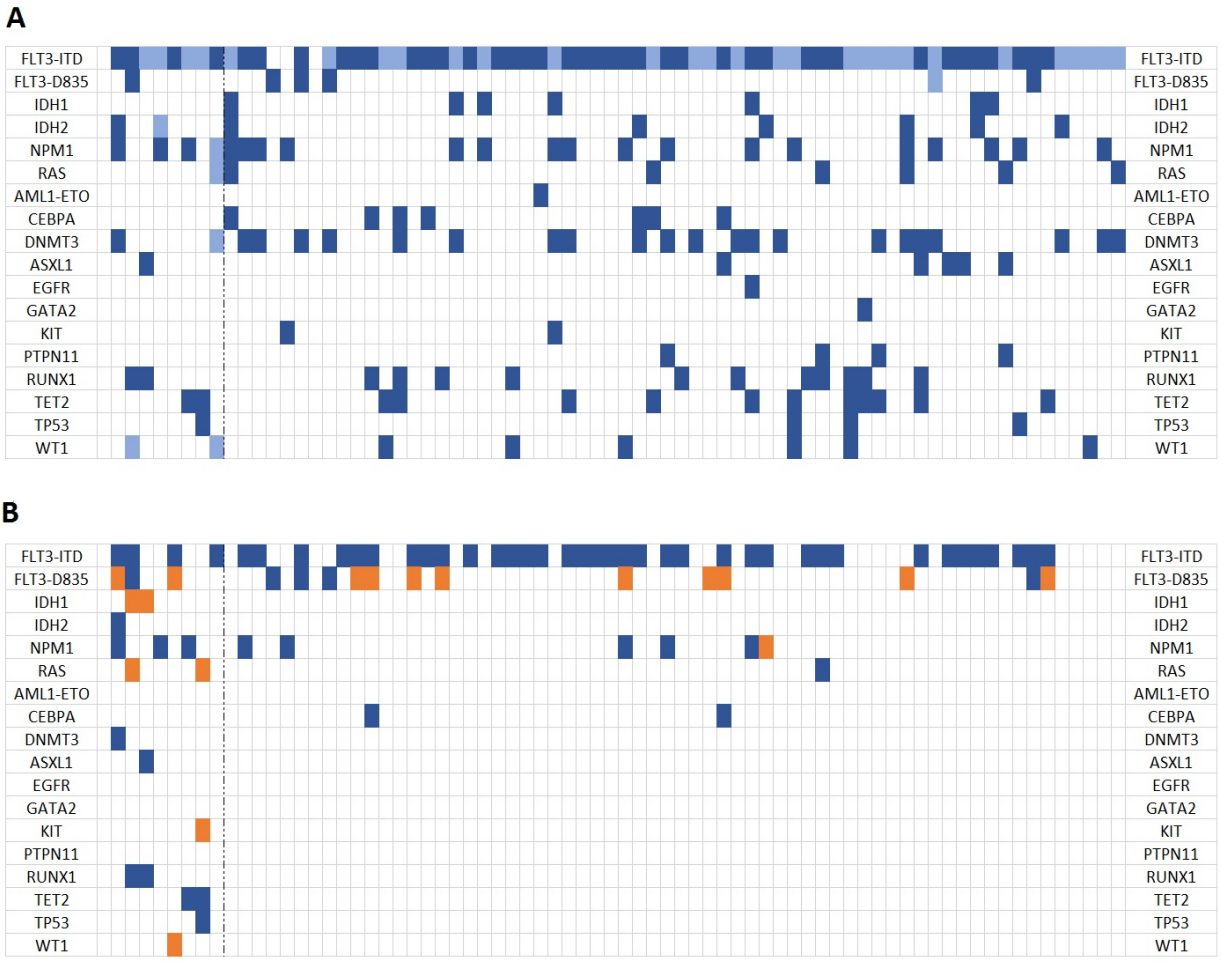
Abbreviations: AML, acute myeloid leukemia; sAML, secondary AML; AZA, azacitidine; LDAC, low-dose cytarabine; PS, performance status.

Supplemental Figure 2: Association between composite response and covariates in previously treated patients (n=39).



Abbreviations: AML, acute myeloid leukemia; sAML, secondary AML; R/R AML, relapsed/refractory AML; AZA, azacitidine; LDAC, low-dose cytarabine; PS, performance status.

Supplemental Figure 3: Comparison of mutations at baseline and at the time of relapse/loss of response in evaluable patients.



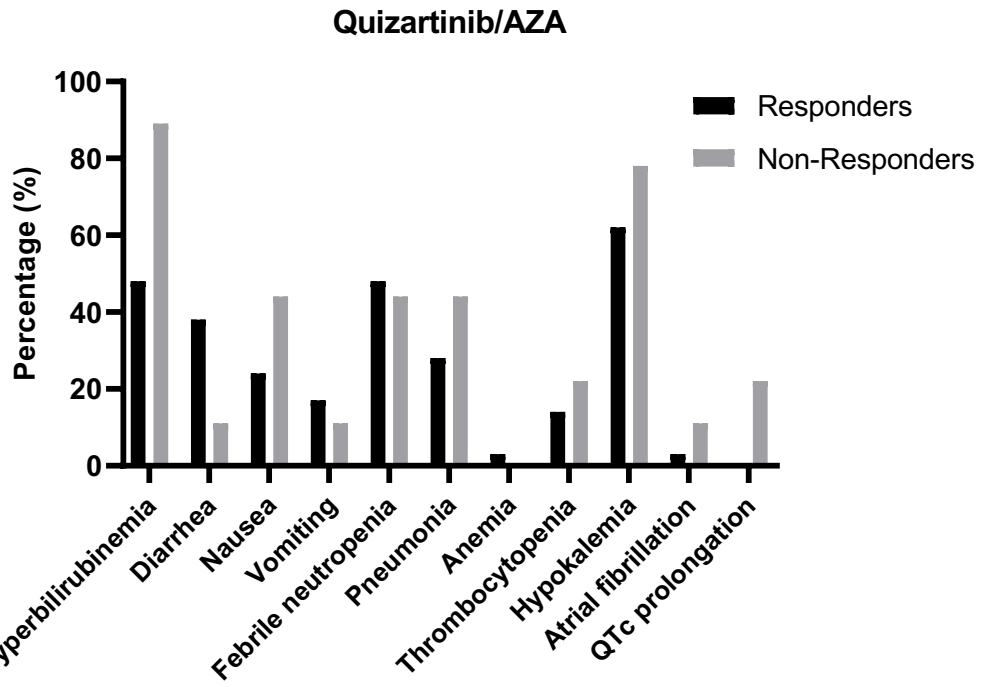
A, At start of treatment; B, at the time of treatment discontinuation. Each column represents one patient. Colors; blue – refers to pre-treatment mutations, light-blue – refers to mutations not present post-treatment, orange – represents newly acquired mutations. The black broken vertical line separates the nine patients evaluated with 81 gene panel after treatment discontinuation.

At the time of treatment discontinuation; 66 patients had *FLT3* mutation assessed.

Other than *FLT3* mutation; 9 – had 81 gene panel, 15 – had only *NPM1* mutation assessed, 2 – only *RA*S and CEBPA mutations assessed, 2 – only *DNMT3A* mutation assessed.

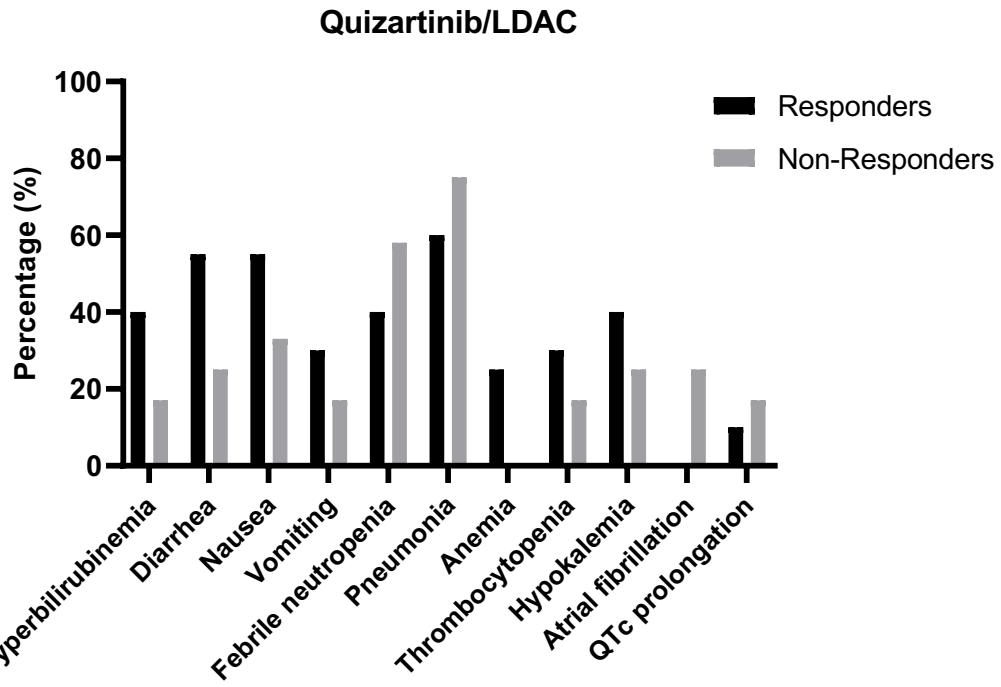
Twenty-nine patients had no molecular assessment.

Supplemental Figure 4: Incidence of treatment emergent adverse events for quizartinib/AZA patients by treatment response.



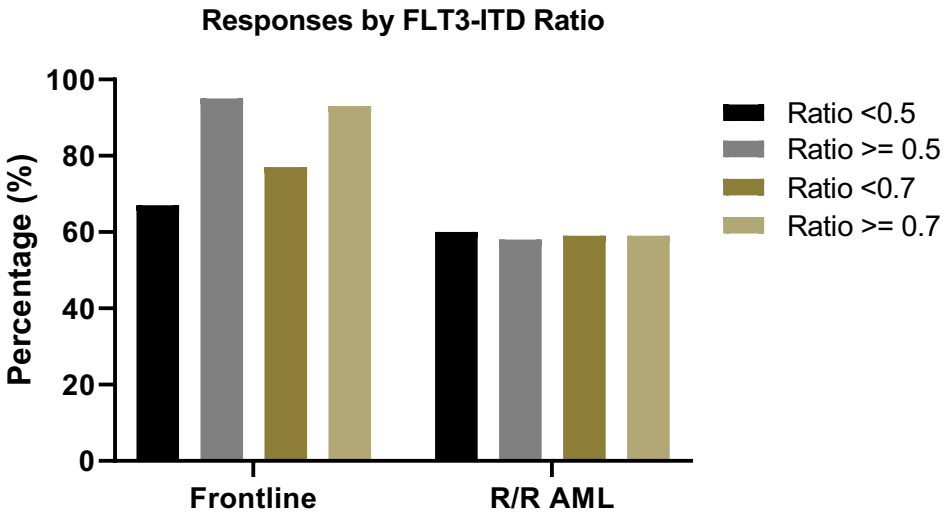
Abbreviations: AZA, azacitidine.

Supplemental Figure 5: Incidence of treatment emergent adverse events for quizartinib/LDAC patients by treatment response.



Abbreviations: LDAC, low-dose cytarabine

Supplemental Figure 6: Composite response by FLT3-ITD ratio in all patients (n=73).



Abbreviations: R/R AML, relapsed/refractory acute myeloid leukemia.

Supplemental Table 1: Comparison of responders and non-responders among frontline patients*.

Covariates	Responders Median (Range) N=27	Non-Responders Median (Range) N=5	P-value
WBC	3.1 (2.2 - 19.6)	6.4 (1.1 - 41.6)	0.8369
Platelets	20 (14 - 105)	34 (7 - 377)	0.4721
Hemoglobin	9.5 (8.1 - 11.4)	9 (7 - 10.9)	0.3968
PB Blast%	8 (6 - 35)	21 (0 - 97)	0.2035
BM Blast%	43 (17 - 87)	56 (15 - 97)	0.6997
FLT3-ITD ratio	0.06 (0.01 - 0.86)	0.75 (0.02 - 5.37)	0.0414
Age	74.75 (57.51 - 78.25)	70.76 (57.75 - 82.17)	0.9589

Abbreviations: WBC, white blood cell count; PB, peripheral blood; BM, bone marrow.

*Only patients who completed one cycle of study treatment.

Supplemental Table 2: Univariate analysis for overall survival and relapse free survival in frontline patients*.

Covariates	Level	OS				RFS			
		N	Median (95%CI) (M)	OS Rate at 1 Year (95%CI)	P-value	N	Median (95%CI) (M)	RFS Rate at 1 Year (95%CI)	P-value
	Frontline	32	15.36 (9.9, 21.73)	0.538 (0.386, 0.749)		27	8 (6.37, 18.24)	0.323 (0.178, 0.58)	
Diagnosis Group	AML	9	15.36 (9.9, NA)	0.556 (0.31, 0.997)	0.531	8	8 (3.97, NA)	0.146 (0.024, 0.89)	0.572
	AMML	3	21.73 (9.22, NA)	0.667 (0.3, 1)		3	21.73 (9.22, NA)	0.667 (0.3, 1)	
	AMOL	2	36.97 (18.85, NA)	1 (1, 1)		2	13.19 (NA, NA)	1 (1, 1)	
	RAEB	1	NA (NA, NA)			1	NA (NA, NA)		
	sAML	17	10.85 (7.63, 25.25)	0.443 (0.256, 0.768)		13	6.75 (5.12, NA)	0.252 (0.095, 0.669)	
Diagnosis	AML	15	18.85 (10.88, NA)	0.646 (0.439, 0.951)	0.128	14	9.22 (8, NA)	0.38 (0.178, 0.813)	0.167
	sAML	17	10.85 (7.63, 25.25)	0.443 (0.256, 0.768)		13	6.75 (5.12, NA)	0.252 (0.095, 0.669)	
Regimen	Quizartinib/AZA	14	19.19 (12.37, NA)	0.769 (0.571, 1)	0.025	13	10.54 (8, NA)	0.422 (0.203, 0.875)	0.045
	Quizartinib/LDAC	18	8.51 (7.49, 25.25)	0.361 (0.192, 0.681)		14	6.37 (3.97, NA)	0.232 (0.086, 0.625)	
PS	0	5	19.19 (7.63, NA)	0.6 (0.293, 1)	0.852	4	12.32 (2.75, NA)	0.5 (0.188, 1)	0.755
	1	22	15.9 (10.1, 26.41)	0.556 (0.376, 0.822)		19	9.02 (6.75, NA)	0.321 (0.157, 0.658)	
	2	5	7.49 (6.95, NA)	0.4 (0.137, 1)		4	6.93 (4.95, NA)		
CRc	No	5	5.86 (4.14, NA)	0.2 (0.035, 1)	0.001				
	Yes	27	16.2 (10.85, 25.39)	0.603 (0.439, 0.828)					
IDH1	Neg	29	15.36 (9.22, 21.73)	0.562 (0.403, 0.783)	0.7	24	9.02 (6.75, 19.19)	0.367 (0.206, 0.654)	< 0.0001
	Pos	3	10.85 (9.9, NA)	0.333 (0.067, 1)		3	2.75 (1.19, NA)		
IDH2	Neg	30	12.37 (9.22, 21.73)	0.505 (0.35, 0.729)	0.772	25	8 (6.37, 19.19)	0.304 (0.159, 0.584)	0.556
	Pos	2	22.05 (18.85, NA)	1 (1, 1)		2	7.97 (2.75, NA)	0.5 (0.125, 1)	
NPM1	Neg	23	15.36 (10.1, 25.39)	0.577 (0.4, 0.831)	0.991	19	8 (6.75, 21.73)	0.332 (0.165, 0.667)	0.233
	Pos	9	10.85 (9.22, NA)	0.444 (0.214, 0.923)		8	3.97 (2.75, NA)	0.3 (0.095, 0.943)	
DNMT3A	Neg	22	10.1 (7.63, 25.39)	0.435 (0.267, 0.708)	0.401	17	7.29 (5.12, 22.95)	0.226 (0.087, 0.587)	0.422
	Pos	10	18.85 (15.36, NA)	0.778 (0.549, 1)		10	13.19 (9.22, NA)	0.514 (0.262, 1)	
ASXL1	Neg	26	12.37 (9.9, 21.73)	0.521 (0.358, 0.759)	0.431	22	9.02 (6.37, 19.19)	0.354 (0.189, 0.664)	0.934
	Pos	5	15.36 (7.49, NA)	0.533 (0.214, 1)		4	7.39 (4.95, NA)	0.25 (0.046, 1)	

Abbreviations: OS, overall survival; RFS, relapse free survival; AML, acute myeloid leukemia; sAML, secondary AML; AZA, azacitidine; LDAC, low-dose cytarabine; PS, performance status; CRc, composite response; HR, hazard ratio.

*Only patients who completed one cycle of study treatment.

Supplemental Table 3: Comparison of responders and non-responders in previously treated patients*.

Covariates	Responders Median (Range) N=20	Non-Responders Median (Range) N= 18	P-value
WBC	5.35 (0.7 - 60.5)	5.4 (0.5 -31.7)	0.5918
Platelets	28.5 (10 - 174)	23.5 (4 - 454)	0.9190
Hemoglobin	9.5 (8 - 12.8)	9.05 (7.6 - 10.2)	0.0290
PB Blast%	43 (0 - 97)	71 (0 - 99)	0.1644
BM Blast%	60.5 (13 - 95)	75 (15 - 98)	0.5054
FLT3-ITD ratio	0.72 (0.07 - 3.69)	0.74 (0.01 - 2.48)	0.6153
Age	62.76 (24.85 - 83.8)	68.72 (23.57 - 78.97)	0.4434

Abbreviations: CRc, composite response; WBC, white blood cell count; PB, peripheral blood; BM, bone marrow; N, no; Y, yes.

*Only patients who completed one cycle of study treatment.

Supplemental Table 4: Univariate analysis for overall survival and relapse-free survival in previously treated patients*.

Covariates	Level	OS				RFS			
		N	Median (95%CI) (M)	OS Rate at 1 Year (95%CI)	P-value	N	Median (95%CI)	RFS Rate at 1 Year (95%CI)	P-value
Previously treated		38	6.2 (4.61, 15.29)	0.363 (0.235, 0.559)		22	5.76 (4.07, 9.15)	0.133 (0.037, 0.473)	
Diagnosis Group	AML	24	10.07 (4.61, 17.36)	0.392 (0.236, 0.652)	0.484	13	6.41 (4.37, NA)	0.138 (0.023, 0.82)	0.756
	AMML	6	5.15 (2.61, NA)	0.333 (0.108, 1)		3	5.76 (2.95, NA)	0.333 (0.067, 1)	
	AMOL	2	4.24 (NA, NA)			2	3.53 (NA, NA)		
	sAML	6	5.19 (2.54, NA)	0.333 (0.108, 1)		4	5.88 (2.54, NA)		
Diagnosis	AML	32	8.61 (4.54, 15.29)	0.368 (0.23, 0.588)	0.585	18	5.76 (3.53, NA)	0.18 (0.053, 0.612)	0.675
	sAML	6	5.19 (2.54, NA)	0.333 (0.108, 1)		4	5.88 (2.54, NA)		
Regimen	Quizartinib /Aza	24	12.85 (5.76, 18.07)	0.502 (0.331, 0.761)	0.089	16	5.76 (3.53, NA)	0.179 (0.052, 0.619)	0.812
	Quizartinib /LDAC	14	4 (2.75, 19.73)	0.143 (0.04, 0.515)		6	6.14 (2.54, NA)		
PS	0	5	5.25 (4.24, NA)	0.4 (0.137, 1)	0.292	2	5.61 (3.53, NA)		0.919
	1	24	10.07 (5.12, 17.36)	0.393 (0.236, 0.653)		16	5.14 (4.07, NA)	0.1 (0.016, 0.623)	
	2	9	4 (2.75, NA)	0.25 (0.075, 0.83)		4	7.39 (1.39, NA)	0.375 (0.084, 1)	
CRc	No	18	3.1 (2.61, 10.54)	0.167 (0.059, 0.468)	0.002	2	5.37 (2.54, NA)		0.773
	Yes	20	14.07 (8.61, 20.34)	0.556 (0.368, 0.84)		20	5.76 (4.07, 18.07)	0.153 (0.044, 0.534)	
IDH1	Neg	28	8.61 (4.61, 16.03)	0.388 (0.239, 0.629)	0.965	18	4.51 (3.53, NA)	0.079 (0.012, 0.509)	0.398
	Pos	4	3.1 (2.44, NA)	0.25 (0.046, 1)		1	NA (NA, NA)		
IDH2	Neg	27	5.76 (4.24, 16.03)	0.323 (0.183, 0.57)	0.947	16	5.76 (4.07, NA)		0.719
	Pos	5	13.83 (3.8, NA)	0.6 (0.293, 1)		3	2.95 (2.37, NA)	0.333 (0.067, 1)	

NPM1	Neg	18	5.63 (3.8, 19.73)	0.389 (0.218, 0.694)	0.829	11	6.41 (3.53, NA)		0.644
	Pos	12	7.19 (2.81, NA)	0.3 (0.116, 0.773)		8	5.14 (2.95, NA)	0.25 (0.05, 1)	
DNMT3A	Neg	15	12.85 (6.14, 19.76)	0.533 (0.332, 0.856)	0.058	12	6.41 (4.07, NA)	0.11 (0.018, 0.688)	0.307
	Pos	13	3.8 (2.61, NA)	0.188 (0.054, 0.652)		7	4.51 (2.95, NA)		
ASXL1	Neg	22	9.34 (5.12, 17.36)	0.409 (0.248, 0.676)	0.484	16	4.51 (3.53, NA)	0.094 (0.015, 0.587)	0.595
	Pos	1	19.76 (NA, NA)	1 (1, 1)		1	7.69 (NA, NA)		

Abbreviations: OS, overall survival; RFS, relapse-free survival; AML, acute myeloid leukemia; sAML, secondary AML; AZA, azacitidine; LDAC, low-dose cytarabine; PS, performance status; CRc, composite response; HR, hazard ratio.

*Only patients who completed one cycle of study treatment.

Supplementary Table 5: Analysis of overall survival and relapsed-free survival by FLT3-ITD ratio in frontline and relapsed/refractory patients*.

FLT3-ITD ratio	OS Hazard Ratio	Lower	Upper	P-value	RFS Hazard Ratio	Lower	Upper	P-value
Frontline patients								
FLT3-ITD ratio-1 (≥0.5 vs. <0.5)	0.4739	0.2136	1.0512	0.0662	0.9216	0.3681	2.3073	0.8616
FLT3-ITD ratio-2 (≥0.7 vs. <0.7)	0.5630	0.2506	1.2647	0.1642	1.0596	0.4466	2.5137	0.8955
Relapsed/refractory patients								
FLT3-ITD ratio-1 (≥0.5 vs. <0.5)	1.1710	0.5610	2.4439	0.6742	1.5914	0.5620	4.5060	0.3816
FLT3-ITD ratio-2 (≥0.7 vs. <0.7)	1.1029	0.5304	2.2935	0.7931	1.6116	0.5784	4.4906	0.3613

Abbreviations: OS; overall survival; RFS, relapse-free survival; R/R AML, relapsed/refractory acute myeloid leukemia.

*Only patients who completed one cycle of study treatment.

Supplementary Table 6: Analysis of association between response and covariates by univariate logistic regression model in all patients*.

Variable	P-value	Odds Ratio	95% CI Low	95% CI High
WBC	0.4232	1.0199	0.97188	1.0703
PLT	0.79498	0.99917	0.99296	1.00543
HGB	0.42862	1.22671	0.73963	2.03455
PB Blast%	0.11616	0.98748	0.97208	1.00312
BM Blast%	0.616	0.99491	0.97528	1.01494
FLT3-ITD ratio	0.19667	1.81359	0.73462	4.47731
Age	0.4284	1.0142	0.97942	1.05021
Diagnosis sAML vs AML	0.8104	0.879	0.306	2.523
Regimen Quizartinib+LDAC vs Quizartinib+Aza	0.0784	0.399	0.143	1.11
Prior AML treatment >0 vs 0	0.0069	0.206	0.065	0.648
ECOG PS				
1 vs 0	0.4673	1.692	0.41	6.992
2 vs 0	0.8887	0.889	0.171	4.626
IDH1 Pos vs Neg	0.4247	0.52	0.105	2.588
IDH2 Pos vs Neg	0.9454	1.062	0.187	6.025
NPM1 Pos vs Neg	0.6489	1.324	0.395	4.435
DNMT3a Pos vs Neg	0.8782	0.911	0.275	3.011
ASXL1 Pos vs Neg	0.7301	1.486	0.157	14.095
TET2 Pos vs Neg	0.0069	0.147	0.037	0.591

Abbreviations: WBC, white blood cell count; PLT, platelet count; HGB, hemoglobin; PB, peripheral blood; BM, bone marrow; sAML, secondary AML; PS, performance status.

*Only patients who completed one cycle of study treatment.

Supplementary Table 7: Analysis of association between response and covariates by multivariate logistic regression model in all patients*.

	Full model					Reduced model			
Parameters	OR	95% CI of OR		P value		OR	95% CI		P value
Prior AML treatment >0 vs 0	0.359	0.06	2.279	0.2773					
Regimen Quizartinib+LDAC vs Quizartinib+Aza	0.206	0.04	1.107	0.0656					
TET2 Pos vs Neg	0.188	0.04	0.953	0.0436		0.147	0.037	0.591	0.0069
FLT3-ITD ratio	1.254	0.39	4.055	0.7055					
PB Blast%	0.984	0.96	1.012	0.2578					

Abbreviations: LDAC, low-dose cytarabine; Aza, azacitidine; PB, peripheral blood.

*Only patients who completed one cycle of study treatment.