Supplement

Table S1. Definitions of Response Parameters

Response Parameter	Definition
Complete remission (CR)	Presence of regenerating hematopoietic cells in the bone marrow and achievement of a morphologic leukemia-free state with absolute neutrophil count (ANC) ≥1 × 10^9/L, platelet count ≥100 × 10^9/L, normal bone marrow differential with <5% blasts, and red blood cell (RBC)/platelet transfusion independence with no evidence of extramedullary leukemia.
Complete remission with partial hematologic recovery (CRh)	Bone marrow blasts <5% with partial hematologic recovery defined as ANC ≥0.5 × 10^9/L and platelet count ≥50 × 10^9/L, with no evidence of extramedullary leukemia and cannot be classified as CR.
Complete remission with incomplete platelet recovery (CRp)	Achievement of all CR criteria except for platelet recovery (platelet count <100 × 10^9/L).
Complete remission with incomplete hematologic recovery (CRi)	Achievement of all CR criteria except for hematologic recovery with residual neutropenia (ANC <1 × 10^9/L) with or without RBC/platelet transfusion independence.
Composite complete remission (CRc)	Achievement of CR, CRi, or CRp.
Partial remission (PR)	Presence of regenerating normal hematopoietic cells in bone marrow with evidence of peripheral recovery with no (or only a few regenerating) circulating blasts and with a ≥50% decrease in the number of blasts in the bone marrow aspirate with total marrow blasts between 5% and 25%. A value of ≤5% blasts is also considered a PR if Auer rods are present.

Relapse	• Relapse after CR, CRh, CRp, or CRi
	  o Reappearance of leukemic blasts in the peripheral blood and a ≥5% increase in the percentage of blasts that is not attributable to any other cause, or reappearance or new appearance of extramedullary leukemia
	• Relapse after PR
	  o Reappearance of significant numbers of peripheral blasts and an increase in the percentage of blasts in the bone marrow aspirate to >25% not attributable to any other cause, or reappearance or new appearance of extramedullary leukemia

Overall survival (OS)	Time from the date of randomization until the date of death from any cause. For subjects who are not known to have died by the end of study follow-up, OS was censored at the date of last contact.
Event-free survival (EFS)	Time from the date of randomization until the date of documented relapse (excluding relapse after PR), treatment failure, or death, whichever occurs first. For subjects who are not known to have had a relapse, treatment failure, or death event, EFS was censored at the date of last relapse-free disease assessment.

Table S2. Study Drug Exposure in Patients With *FLT3*$^{+}$ R/R AML Treated With Gilteritinib

Exposure Parameter	Exposure Duration			Total (N=246)
	<6 Months (n=161)	≥6 to <12 Months (n=37)	≥12 Months (n=48)	
Median duration of exposure, months (IQR)	2.53 (1.81-3.98)	7.69 (6.74-9.00)	25.53 (14.92-34.02)	4.14 (2.14-8.21)
Median number of cycles (range)	3 (1-7)	9 (7-13)	28 (13-52)	5 (1-52)
Dosing, n (%) Increases Decreases Interruptions	 51 (31.7) 38 (23.6) 64 (39.8)	 16 (43.2) 15 (40.5) 22 (59.5)	 11 (22.9) 24 (50.0) 36 (75.0)	 78 (31.7) 77 (31.3) 122 (49.6)
Median dose intensity, mg/day	120.0	120.0	118.1	120.0
Median relative dose intensity, %	100.00	100.00	98.45	100.00
Median cumulative dose, mg (range)	9080 (480-28,360)	27,000 (11,880-56,160)	73,720 (27,360-194,280)	14,200 (480-194,280)
Median average daily dose, mg/day (range)	120.0 (81.9-180.5)	120.0 (49.9-192.3)	120.0 (42.4-193.1)	120.0 (42.4-193.1)

Abbreviations: AML, acute myeloid leukemia; IQR, interquartile range; R/R, relapsed or refractory; SAF, safety analysis set.

Table S3. Baseline Characteristics of Patients in the Gilteritinib Arm Who Remained Alive for ≥2 Years Without Relapse

Characteristic	Duration of Gilteritinib Therapy		Total (N=26)
	≤1 Year (n=7)	>1 Year (n=19)	
Median age, years (range)	55 (34-67)	54 (33-71)	54.5 (33-71)
Age <65 years, n (%)	6 (86)	16 (84)	22 (85)
Female, n (%)	5 (71)	12 (63)	17 (65)
Baseline ECOG status 0-1, n (%)	7 (100)	18 (95)	25 (96)
FLT3 mutation type, n (%)			
FLT3-ITD	6 (86)	17 (89)	23 (88)
FLT3-TKD	1 (14)	1 (5)	2 (8)
FLT3-ITD and TKD	0	1 (5)	1 (4)
Cytogenetic risk status, n (%)			
Favorable	0	1 (5)	1 (4)
Intermediate	6 (86)	14 (74)	20 (77)
Unfavorable	1 (14)	1 (5)	2 (8)
Other	0	3 (16)	3 (12)
Response to first-line therapy per IRT			
Relapse ≤6 months after allogeneic HSCT	1 (14)	2 (11)	3 (12)
Relapse ≤6 months after CRc and no HSCT	1 (14)	6 (32)	7 (27)
Relapse >6 months after allogeneic HSCT	1 (14)	5 (26)	6 (23)
Relapse >6 months after CRc and no HSCT	3 (43)	1 (5)	4 (15)
Primary refractory without HSCT	1 (14)	5 (26)	6 (23)
Pre-selected salvage chemotherapy, n (%)			
High intensity	7 (100)	13 (68)	20 (77)
Low intensity	0	6 (32)	6 (23)
Prior HSCT, n (%)			
Yes	2 (29)	7 (37)	9 (35)
No	5 (71)	12 (63)	17 (65)
Prior anthracycline use, n (%)			
Yes	6 (86)	19 (100)	25 (96)
No	1 (14)	0	1 (4)
Prior FLT3 inhibitor			
Midostaurin	0	0	0
Sorafenib	0	1	1
FLT3-ITD allelic ratio, n (%)			
High	4 (57)	8 (42)	12 (46)
Low	2 (29)	10 (53)	12 (46)
Missing	1 (14)	1 (5)	2 (8)
Co-mutations			
NPM1	4 (57)	8 (42)	12 (46)
DNMT3A	3 (43)	6 (32)	9 (35)
DNMT3A and *NPM1*	3 (43)	6 (32)	9 (35)
WT1	1 (14)	3 (16)	4 (15)
IDH1 or *IDH2*	0	2 (11)	2 (8)

Abbreviations: CRc, composite complete remission; ECOG, Eastern Cooperative Oncology Group; HSCT, hematopoietic stem cell transplantation; IRT, interactive response technology; ITD, internal tandem duplication; TKD, tyrosine kinase domain.

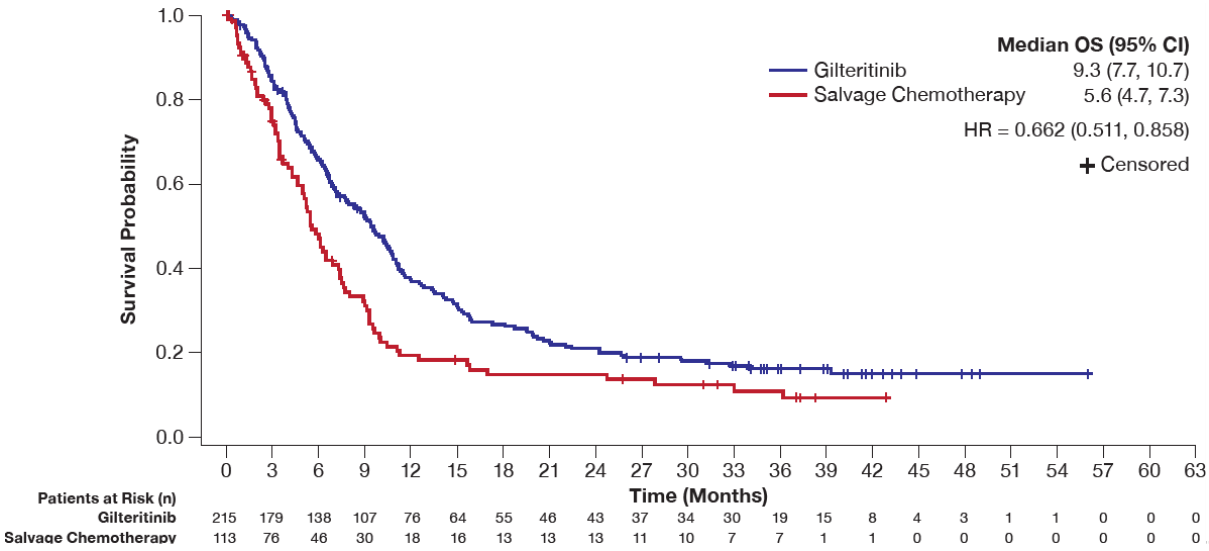
Table S4. Baseline Characteristics of Patients in the Gilteritinib Arm Who Remained Alive for ≥2 Years Without Relapse Without HSCT

Characteristic	N=8
Median age, years (range)	54.5 (42-68)
Age <65 years, n (%)	7 (87.5)
Female, n (%)	6 (75.0)
FLT3 mutation type, n (%)	
FLT3-ITD	7 (87.5)
FLT3-TKD	0
FLT3-ITD and TKD	1 (12.5)
Relapse status per IRT	
Relapse ≤6 months after allogeneic HSCT	3 (37.5)
Relapse >6 months after allogeneic HSCT	4 (50.0)
Relapse >6 months after CRc without HSCT	1 (12.5)
Pre-selected salvage chemotherapy, n (%)	
High intensity	5 (62.5)
Low intensity	3 (37.5)
Prior HSCT, n (%)	
Yes	7 (87.5)
No	1 (12.5)
FLT3-ITD allelic ratio, n (%)	
High	3 (37.5)
Low	5 (62.5)
Co-mutations	
NPM1	5 (62.5)
DNMT3A	3 (37.5)
DNMT3A and *NPM1*	3 (37.5)
WT1	0
IDH1 or *IDH2*	4 (50.0)

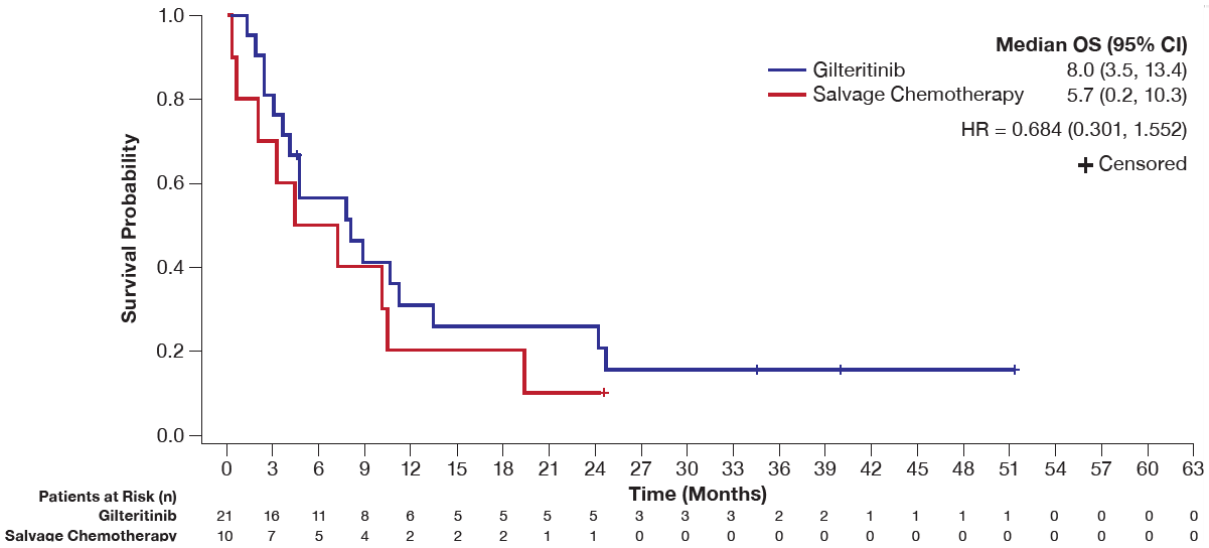
Abbreviations: HSCT, hematopoietic stem cell transplantation; IRT, interactive response technology; ITD, internal tandem duplication; TKD, tyrosine kinase domain.

Figure S1. Overall Survival

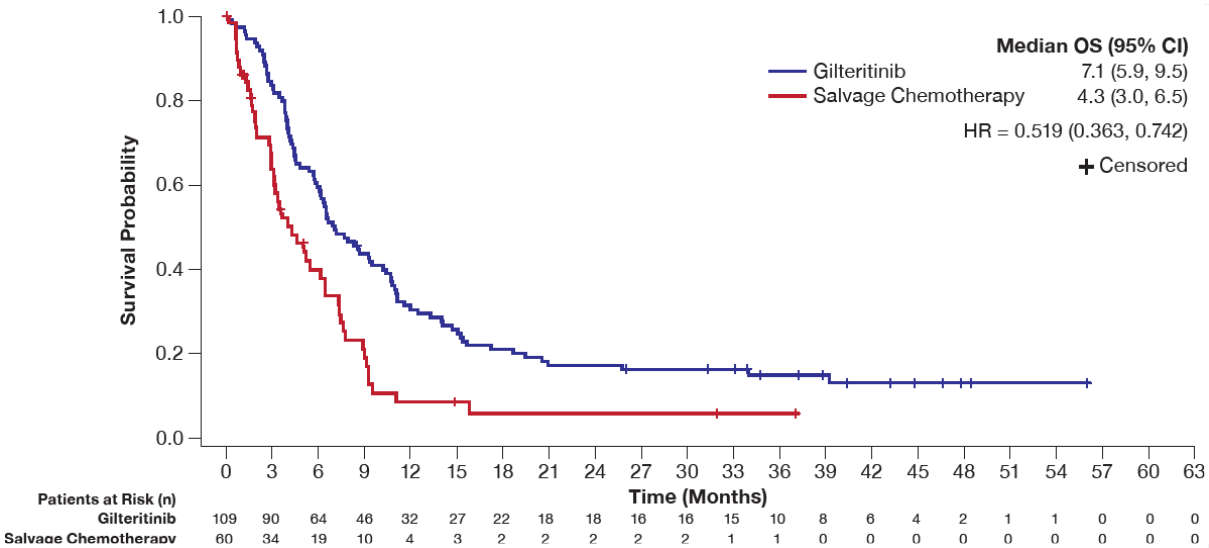
A. Patients With *FLT3*-ITD Mutations Only[a]



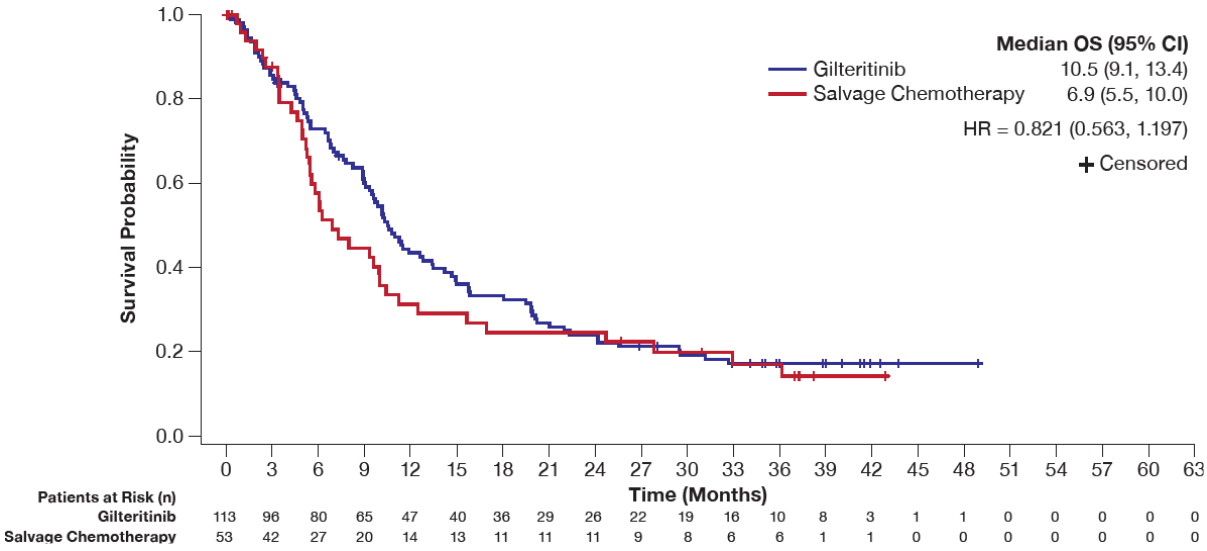
B. Patients With *FLT3*-TKD Mutations Only[a]



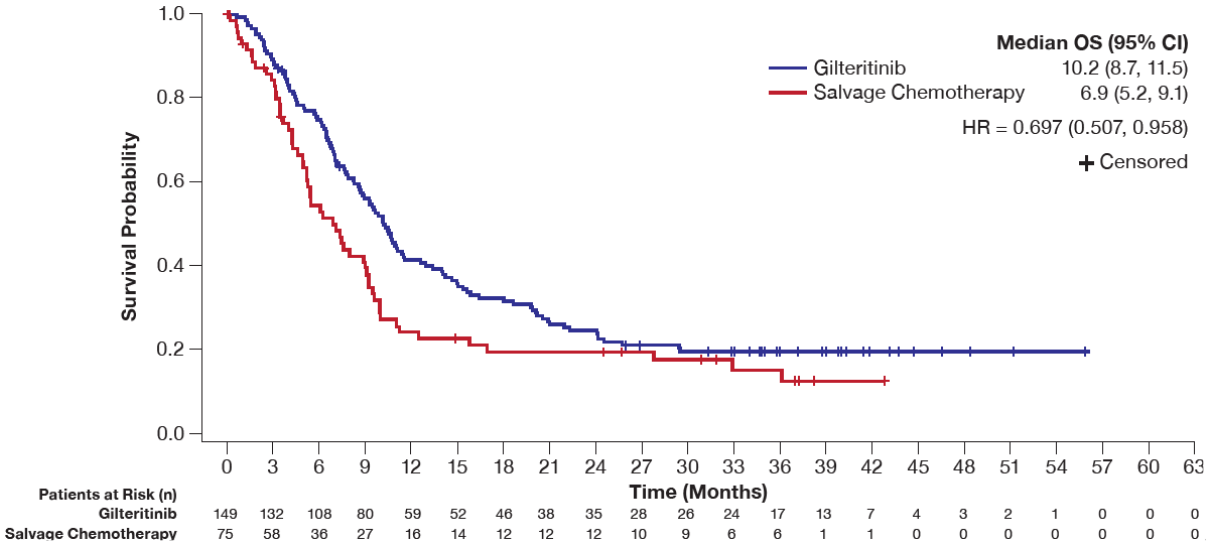
C. Patients With a High *FLT3*-ITD Allelic Ratio[b]



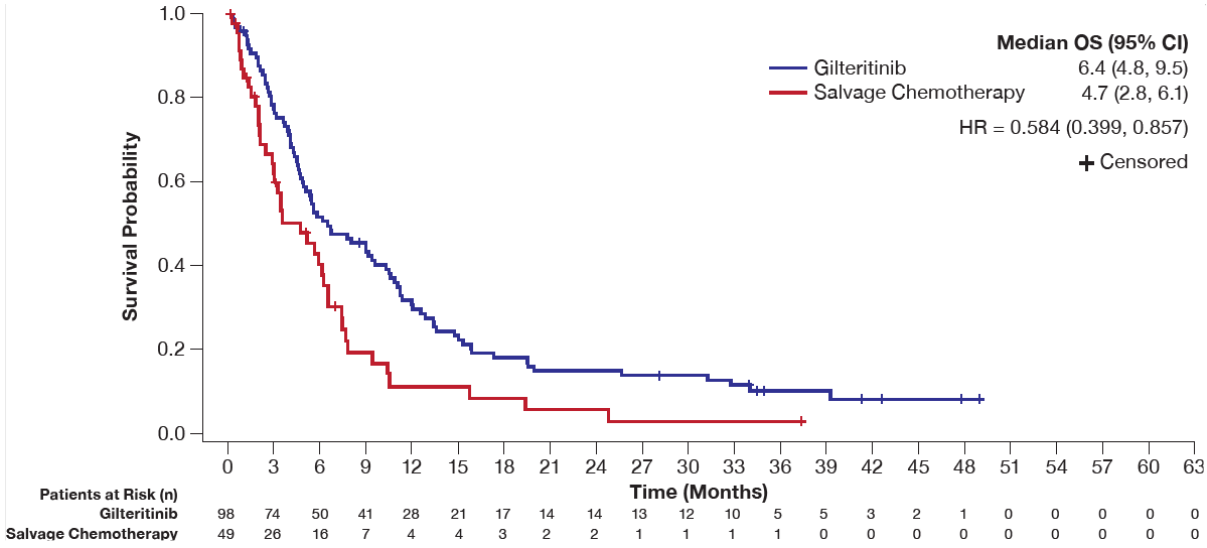
D. Patients With a Low *FLT3*-ITD Allelic Ratio[b]



E. Patients Pre-selected for High-Intensity Chemotherapy per IRT



F. Patients Preselected for Low-Intensity Chemotherapy per IRT

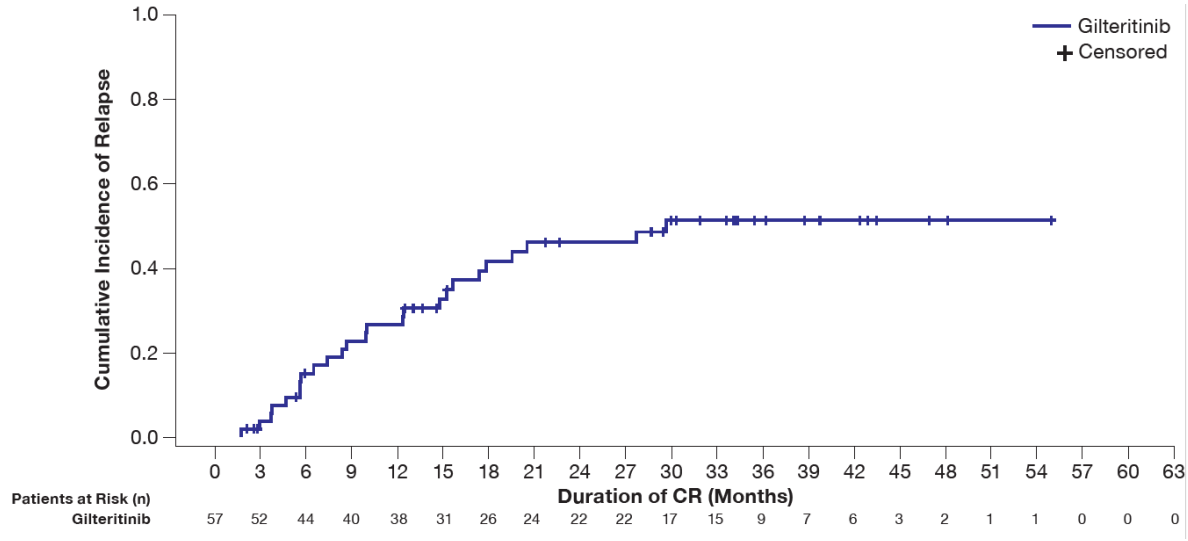


[a]Mutation confirmed by central laboratory testing.

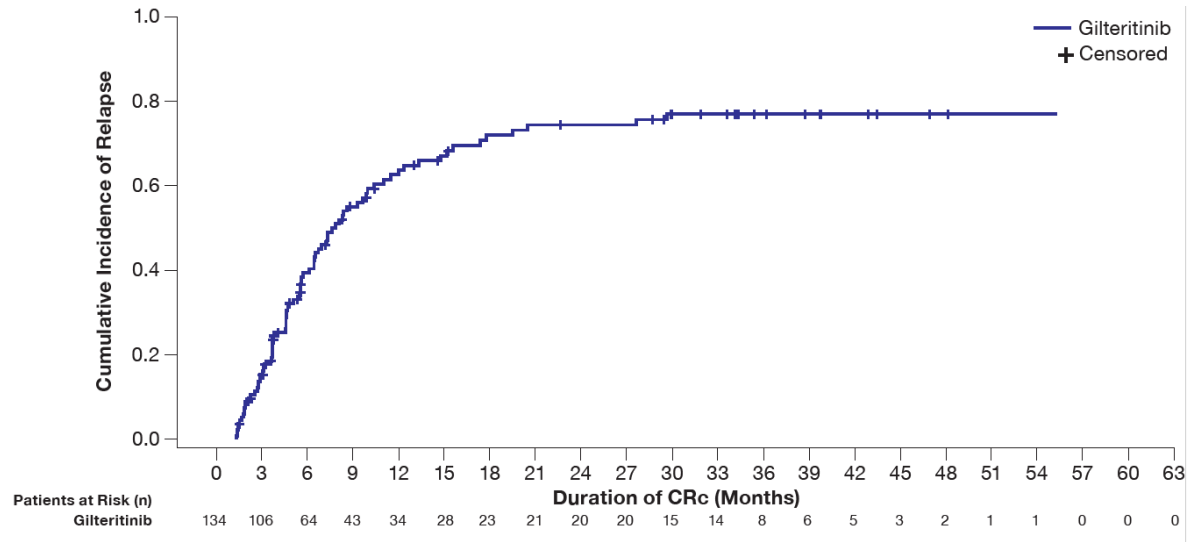
[b]A high allelic ratio was defined as being greater than or equal to the median value of 0.77.
Abbreviations: CI, confidence interval; HR, hazard ratio; IRT, interactive response technology; ITD, internal tandem duplication; OS, overall survival; TKD, tyrosine kinase domain.

Figure S2. Cumulative Incidence of Relapse in Patients Treated With Gilteritinib: Time From Randomization to Relapse

A. Relapse After CR

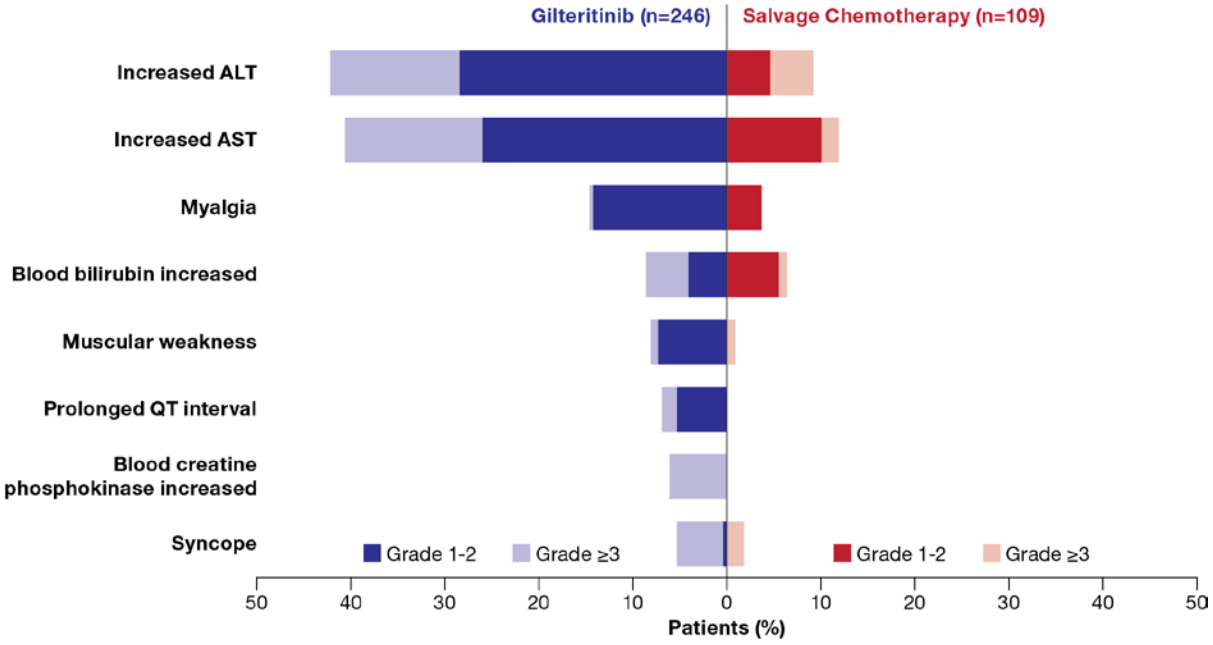


B. Relapse After CRc



Abbreviations: CR, complete remission; CRc, composite complete remission.

Figure S3. Adverse Events of Interest in ≥5% of Patients With *FLT3*⁺ R/R AML in Any Treatment Arm



Abbreviations: ALT, alanine aminotransferase; AML, acute myeloid leukemia; AST, aspartate aminotransferase; R/R, relapsed or refractory.