

Clinical Outcomes in Patients With Relapsed/Refractory Acute Myeloid Leukemia Treated With Gilteritinib Who Received Prior Midostaurin or Sorafenib

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INTRODUCTION

- Gilteritinib is an oral FLT3 inhibitor approved for the treatment of *FLT3*-mutated relapsed or refractory (R/R) acute myeloid leukemia (AML)^{1,2} based on its demonstrated clinical benefit in this patient population^{3,4}
 - The phase 1/2 CHRYSLIS trial demonstrated the safety and antileukemic activity of gilteritinib in a *FLT3*-mutation-enriched R/R AML population³
 - The phase 3 ADMIRAL trial demonstrated the superiority of gilteritinib to salvage chemotherapy (SC) in patients with *FLT3*-mutated R/R AML based on a longer median overall survival (OS) with gilteritinib (9.3 vs 5.6 months; hazard ratio [HR]=0.64 [95% CI: 0.49, 0.83]; *P*<0.001)⁴
- The efficacy of gilteritinib in patients with prior tyrosine kinase inhibitor (TKI) therapy is not clearly defined
- We assessed whether prior TKI therapy affected response and survival in these two trials

METHODS

CHRYSLIS and ADMIRAL Study Designs

- CHRYSLIS was a global phase 1/2 dose-escalation/expansion study in which patients with R/R AML were enrolled across seven dose-escalation cohorts to receive 20-, 40-, 80-, 120-, 200-, 300-, and 450-mg/day gilteritinib³
 - Patients in the CHRYSLIS trial had received at least one line of prior AML therapy³
- ADMIRAL was a global phase 3 study of gilteritinib versus SC in patients with *FLT3*-mutated R/R AML⁴
 - Patients were randomized 2:1 to receive 120-mg gilteritinib or preselected high- or low-intensity chemotherapy⁴
 - Patients in the ADMIRAL trial had received only one line of prior AML therapy⁴

Data Analysis

- A retrospective analysis of clinical outcomes was performed for patients with R/R AML from the CHRYSLIS and ADMIRAL trials who were previously treated with the TKIs midostaurin or sorafenib
- Outcomes were assessed in *FLT3*-mutation-enriched R/R AML patients who received 120- or 200-mg gilteritinib in the CHRYSLIS study and in *FLT3*-mutated R/R AML patients who received 120-mg gilteritinib or SC in the ADMIRAL trial

RESULTS

Patient Populations in the CHRYSLIS and ADMIRAL Trials

- Baseline demographic and disease characteristics were generally similar between the subgroups of patients who were evaluated in the CHRYSLIS and ADMIRAL trials (Table 1)
- Prior treatment characteristics in the 145 patients who received 120- or 200-mg/day gilteritinib in the CHRYSLIS trial showed:
 - Most (76%; n=110) had received at least two lines of prior AML therapy
 - Thirty-three (23%) had received prior TKI therapy with sorafenib; none had received prior treatment with midostaurin
- In the ADMIRAL trial, proportions of patients who received prior TKI therapy were similar in the gilteritinib (13%; n=31/247) and SC (11%; n=14/124) arms
 - Gilteritinib arm: prior midostaurin, 5% (n=13); prior sorafenib, 7% (n=18)
 - SC arm: prior midostaurin, 6% (n=8); prior sorafenib, 5% (n=6)

Table 1. Baseline and Prior Treatment Characteristics of Patients With R/R AML in the CHRYSLIS and ADMIRAL Trials

Characteristic	CHRYSLIS 120-/200-mg Gilteritinib		ADMIRAL 120-mg Gilteritinib vs Salvage Chemotherapy			
	Prior TKI (n=33)	No Prior TKI (n=112)	Gilteritinib		Salvage Chemotherapy	
			Prior TKI (n=31)	No Prior TKI (n=216)	Prior TKI (n=14)	No Prior TKI (n=110)
Median age, years (range)	56 (24-84)	61 (22-87)	55 (20-82)	62 (22-84)	64.5 (34-78)	61 (19-85)
Female, n (%)	18 (55)	59 (53)	12 (39)	119 (55)	8 (57)	62 (56)
ECOG performance status, n (%)						
0-1	22 (67)	87 (78)	23 (74)	183 (85)	13 (93)	92 (84)
≥2	11 (33)	25 (22)	8 (26)	33 (15)	1 (7)	18 (16)
<i>FLT3</i> mutation type, n (%)						
<i>FLT3</i> -ITD only	29 (88)	94 (84)	22 (71)	193 (89)	13 (93)	100 (91)
<i>FLT3</i> -TKD only	0	9 (8)	5 (16)	16 (7)	1 (7)	9 (8)
<i>FLT3</i> -ITD and -TKD	4 (12)	7 (6)	4 (13)	3 (1)	0	0
Other unknown/missing	0	2 (2)	0	4 (2)	0	1 (0.9)
Cytogenetic risk status, n (%)						
Favorable	0	4 (4)	0	4 (2)	0	1 (0.9)
Intermediate	23 (70)	78 (70)	28 (90)	154 (71)	13 (93)	76 (69)
Unfavorable	4 (12)	14 (13)	3 (10)	23 (11)	1 (7)	10 (9)
Other unknown/missing	6 (18)	16 (14)	0	35 (16)	0	23 (21)
Response to first-line therapy, n (%)						
Relapsed	22 (67)	74 (66)	19 (61)	130 (60)	11 (79)	65 (59)
Primary refractory	11 (33)	38 (34)	12 (39)	86 (40)	3 (21)	45 (41)
Prior lines of therapy, n (%)						
1	3 (9)	42 (38)	31 (100)	216 (100)	14 (100)	110 (100)
2	6 (18)	46 (41)	0	0	0	0
≥3	24 (73)	34 (30)	0	0	0	0
Prior HSCT, n (%)						
Yes	14 (42)	34 (30)	10 (32)	38 (18)	4 (29)	22 (20)
No	19 (58)	78 (70)	21 (68)	178 (82)	10 (71)	88 (80)

Abbreviations: AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; HSCT, hematopoietic stem cell transplantation; ITD, internal tandem duplication; R/R, relapsed or refractory; TKD, tyrosine kinase domain; TKI, tyrosine kinase inhibitor.

Response Outcomes by Prior TKI Therapy Status in the CHRYSLIS and ADMIRAL Trials

- In both trials, composite complete remission (CRc) rates of >40% were observed in all gilteritinib-treated patients regardless of prior TKI treatment status (Table 2)
- Regardless of prior TKI therapy, CRc rates in the ADMIRAL trial were higher in gilteritinib-treated patients than in the SC arm

Table 2. Response Outcomes in Patients With R/R AML Based on Prior TKI Therapy Status in the CHRYSLIS and ADMIRAL Trials

Response Parameter, n (%)	CHRYSLIS 120-/200-mg Gilteritinib		ADMIRAL 120-mg Gilteritinib vs Salvage Chemotherapy			
	Prior TKI (n=33)	No prior TKI (n=112)	Gilteritinib		Salvage Chemotherapy	
			Prior TKI (n=31)	No prior TKI (n=216)	Prior TKI (n=14)	No prior TKI (n=110)
CR	1 (3)	16 (14)	6 (19)	46 (21)	0	13 (12)
CRi	10 (30)	25 (22)	5 (16)	58 (27)	3 (21)	11 (10)
CRp	3 (9)	7 (6)	4 (13)	15 (7)	0	0
PR	2 (6)	9 (8)	5 (16)	28 (13)	1 (7)	4 (4)
NR	15 (45)	43 (38)	9 (29)	57 (26)	4 (29)	39 (35)
NE	2 (6)	12 (11)	2 (6)	12 (6)	6 (43)	43 (39)
CRc ^a	14 (42)	48 (43)	15 (48)	119 (55)	3 (21)	24 (22)

Bold font indicates aggregate responses.

^aDefined as the sum of patients who achieved CR, CRi, and CRc.

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; CRc, composite complete remission; CRi, complete remission with incomplete hematologic recovery; CRp, complete remission with incomplete platelet recovery; NE, not evaluable; NR, no response; PR, partial remission; R/R, relapsed or refractory; TKD, tyrosine kinase inhibitor.

- High CRc rates were observed in CHRYSLIS patients with *FLT3*-internal tandem duplication (*FLT3*-ITD) mutations and both *FLT3*-ITD and *FLT3*-tyrosine kinase domain (*FLT3*-TKD) point mutations (Table 3)
- In patients treated with gilteritinib in the ADMIRAL trial, high response rates were achieved regardless of *FLT3* mutation type and receipt of prior TKI therapy (Table 3)

Table 3. Response Outcomes by Prior TKI Status According to *FLT3* Mutation Type in Patients With R/R AML Treated With Gilteritinib

Response Parameter, n (%)	CHRYSLIS: 120-/200-mg Gilteritinib					ADMIRAL: 120-mg Gilteritinib					
	Prior TKI		No Prior TKI		<i>FLT3</i> -ITD and -TKD (n=7)	Prior TKI		No Prior TKI		<i>FLT3</i> -ITD and -TKD (n=3)	<i>FLT3</i> -ITD and -TKD (n=3)
	<i>FLT3</i> -ITD (n=29)	<i>FLT3</i> -TKD (n=4)	<i>FLT3</i> -ITD (n=94)	<i>FLT3</i> -TKD (n=9)		<i>FLT3</i> -ITD (n=22)	<i>FLT3</i> -TKD (n=5)	<i>FLT3</i> -TKD (n=4)	<i>FLT3</i> -ITD (n=193)	<i>FLT3</i> -TKD (n=16)	
CR	1 (3)	0	16 (17)	0	0	2 (9)	2 (40)	2 (50)	42 (22)	2 (13)	0
CRi	8 (28)	2 (50)	20 (21)	1 (11)	4 (57)	4 (18)	0	1 (25)	55 (29)	2 (13)	1 (33)
CRp	3 (10)	0	7 (7)	0	0	3 (14)	1 (20)	0	12 (6)	2 (13)	1 (33)
PR	2 (7)	0	6 (6)	1 (11)	1 (14)	5 (23)	0	0	23 (12)	5 (31)	0
NR	13 (45)	2 (50)	34 (36)	7 (77)	1 (14)	7 (32)	1 (20)	1 (25)	50 (26)	5 (31)	1 (33)
NE	2 (7)	0	11 (12)	0	1 (14)	1 (5)	1 (20)	0	11 (6)	0	0
CRc ^a	12 (41)	2 (50)	43 (46)	1 (11)	4 (57)	9 (41)	3 (60)	3 (75)	109 (57)	6 (38)	2 (67)

Bold font indicates aggregate responses.

^aDefined as the sum of patients who achieved CR, CRi, and CRc.

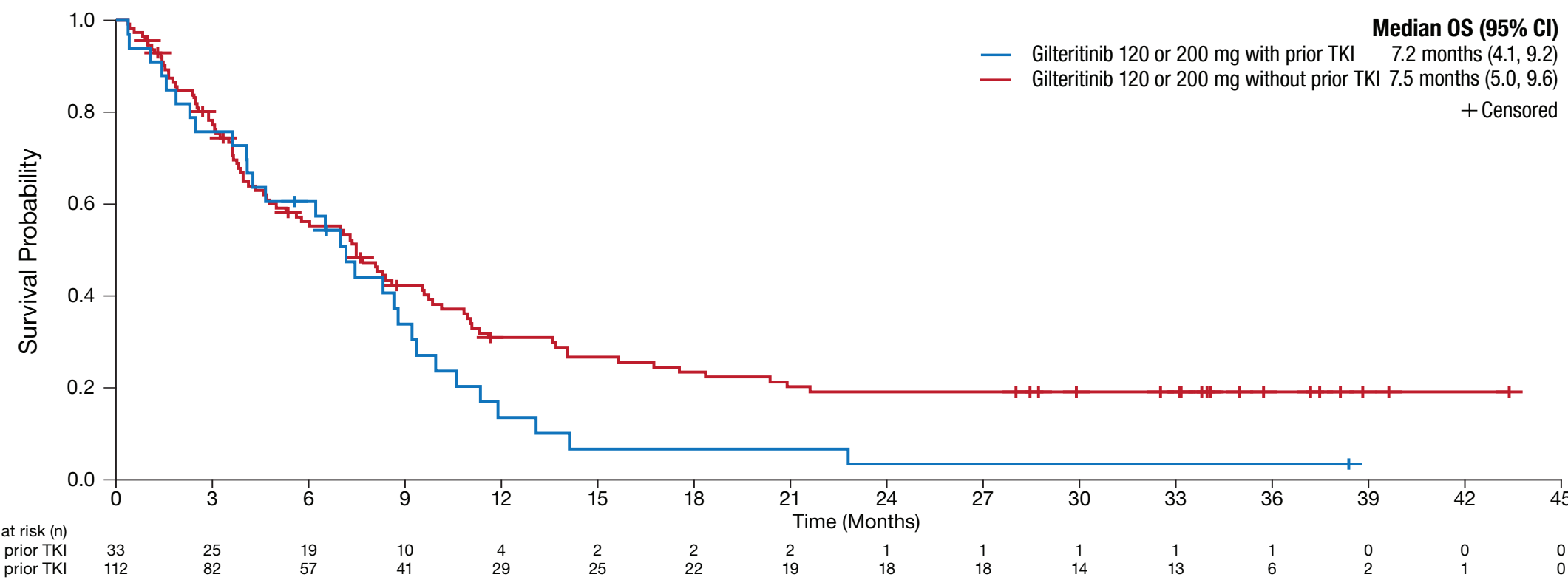
Abbreviations: AML, acute myeloid leukemia; CR, complete remission; CRc, composite complete remission; CRi, complete remission with incomplete hematologic recovery; CRp, complete remission with incomplete platelet recovery; ITD, internal tandem duplication; NE, not evaluable; NR, no response; PR, partial remission; R/R, relapsed or refractory; TKD, tyrosine kinase domain; TKI, tyrosine kinase inhibitor.

Survival Outcomes by Prior TKI Status in the CHRYSLIS and ADMIRAL Trials

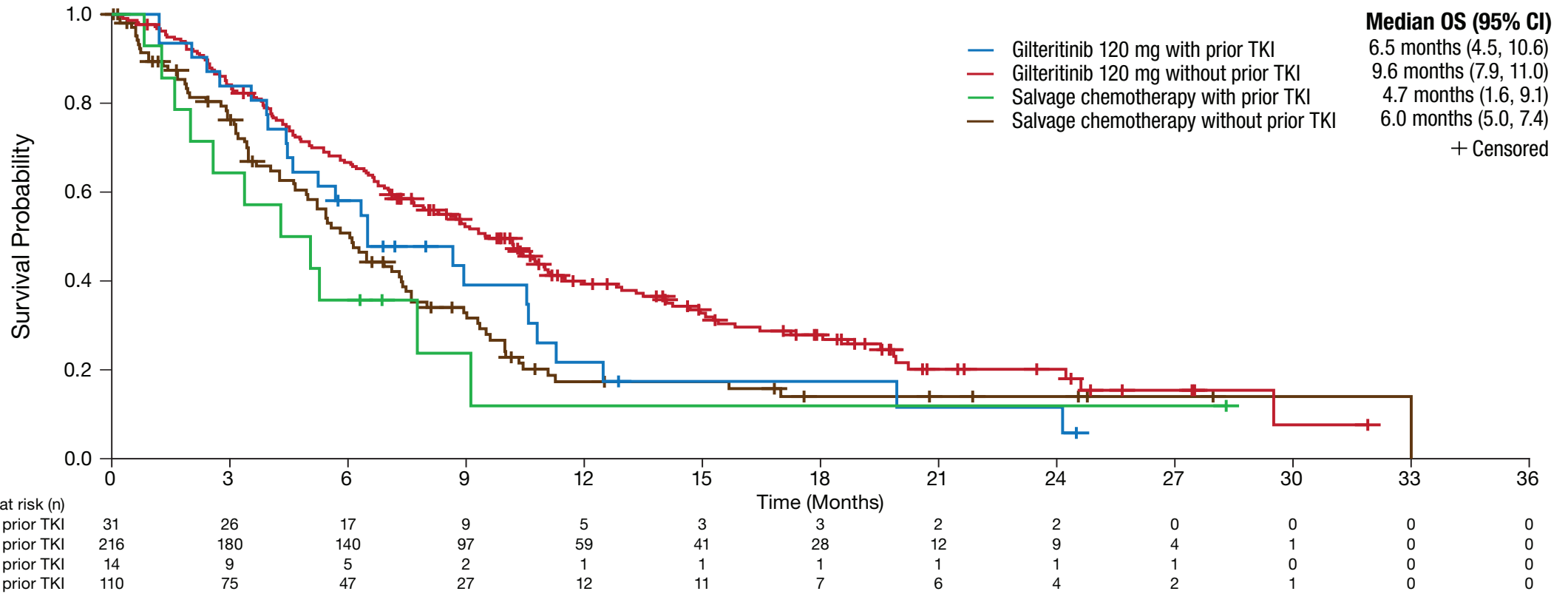
- In the CHRYSLIS trial, median OS was similar in patients regardless of prior TKI therapy (Figure 1A)
- Among patients in the ADMIRAL trial who received prior TKI therapy, OS was longer in patients treated with gilteritinib than those treated with SC (Figure 1B)
- Among patients in the ADMIRAL trial who did not receive prior TKI therapy, survival was longer in patients treated with gilteritinib than in those treated with SC (Figure 1B)

Figure 1. Overall Survival by Prior TKI Status

A. CHRYSLIS Trial



B. ADMIRAL Trial



Median OS, months (95% CI) by <i>FLT3</i> mutation type	CHRYSLIS: 120- or 200-mg Gilteritinib		ADMIRAL: 120-mg Gilteritinib	
	Prior TKI		Prior TKI	
	<i>FLT3</i> -ITD	<i>FLT3</i> -TKD	<i>FLT3</i> -ITD	<i>FLT3</i> -TKD
<i>FLT3</i> -ITD	7.5 (4.1, 9.4)	7.5 (5.0, 10.8)	6.5 (4.4, 10.8)	10.2 (7.7, 11.1)
<i>FLT3</i> -TKD	NA	4.3 (1.8, 8.1)	4.6 (1.2, 24.1)	8.0 (3.0, 24.6)
<i>FLT3</i> -ITD and -TKD	5.6 (1.9, 8.7)	9.6 (1.4, 20.4)	13.2 (4.0, NE)	10.2 (8.9, 20.2)
Relapsed or Refractory Status				
Relapsed			6.5 (4.0, 11.3)	8.9 (6.7, 10.8)
Refractory			10.5 (2.4, 24.1)	10.3 (7.9, 13.5)

Abbreviations: CI, confidence interval; ITD, internal tandem duplication; NA, not applicable; NE, not estimable; OS, overall survival; TKD, tyrosine kinase domain; TKI, tyrosine kinase inhibitor.

Combined Outcomes With Gilteritinib Therapy in the CHRYSLIS and ADMIRAL Trials

- Among all patients who received 120- or 200-mg gilteritinib, similarly high rates of CRc were observed in patients regardless of prior TKI therapy (Table 4)

Table 4. Combined Response Outcomes in Gilteritinib-Treated R/R AML Patients by Prior TKI Status From the CHRYSLIS and ADMIRAL Trials

Response Parameter, n (%)	120 or 200-mg Gilteritinib (N=392)	
	Prior TKI (n=64)	No Prior TKI (n=328)
CR	7 (11)	62 (19)
CRi	15 (23)	83 (25)
CRp	7 (11)	22 (7)
PR	7 (11)	37 (11)
NR	24 (38)	100 (30)
NE	4 (6)	24 (7)
CRc ^a	29 (45)	167 (51)

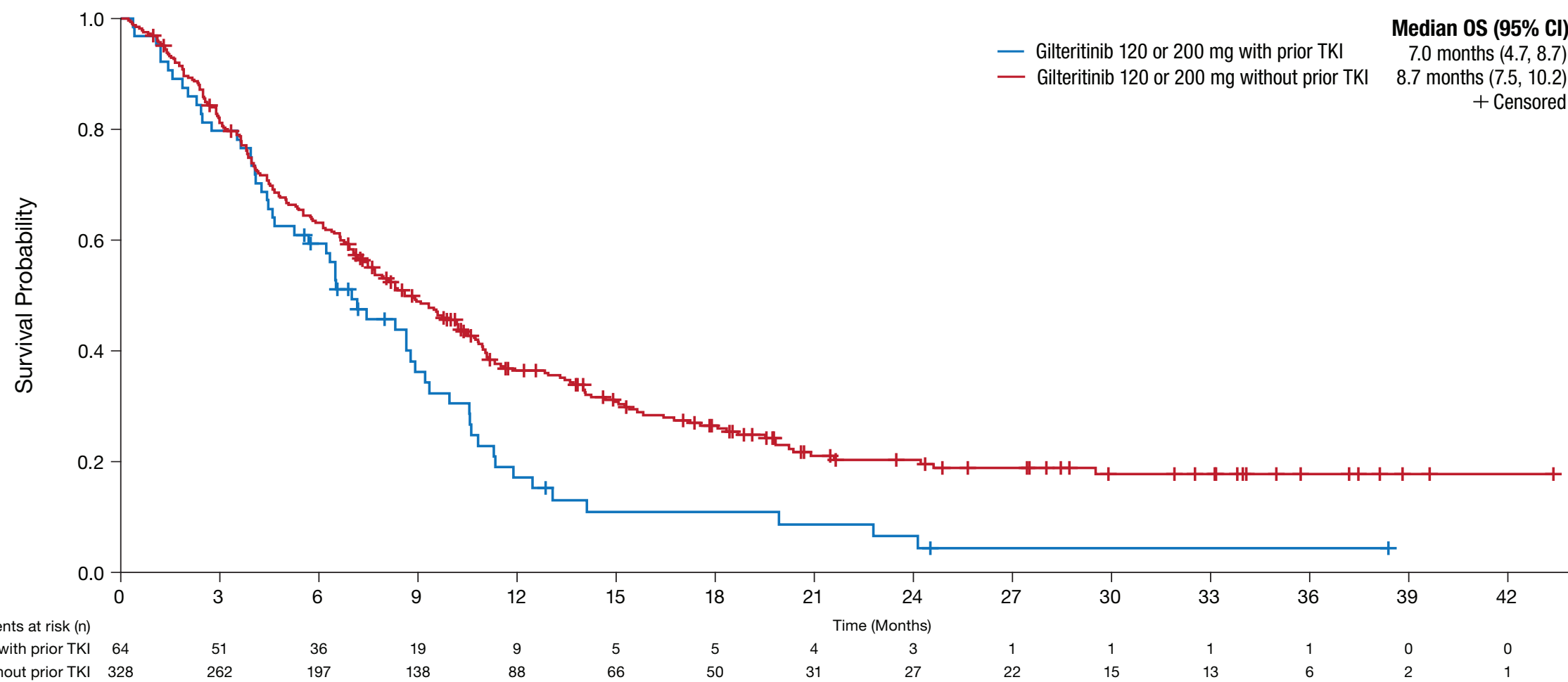
Bold font indicates aggregate responses.

^aDefined as the sum of patients who achieved CR, CRi, and CRc.

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; CRc, composite complete remission; CRi, complete remission with incomplete hematologic recovery; CRp, complete remission with incomplete platelet recovery; NE, not evaluable; NR, no response; PR, partial remission; R/R, relapsed or refractory; TKI, tyrosine kinase inhibitor.

- In the combined analysis of patients treated with gilteritinib from both trials, median OS was longer among patients who did not receive prior TKI therapy than in those who received prior TKI therapy (Figure 2)

Figure 2. Combined Overall Survival by Prior TKI Status in Gilteritinib-Treated Patients From the CHRYSLIS and ADMIRAL Trials



Abbreviations: CI, confidence interval; OS, overall survival; TKI, tyrosine kinase inhibitor.

CONCLUSIONS

- Patients with *FLT3*-mutated R/R AML who received prior midostaurin or sorafenib achieved high remission rates with gilteritinib
 - High response rates with 120- or 200-mg gilteritinib after prior TKI therapy were observed in heavily pretreated patients in the CHRYSLIS trial
 - Higher response rates with gilteritinib than with SC were observed in prior TKI-treated patients in the ADMIRAL trial
 - Remission after prior TKI therapy was achieved in patients with *FLT3*-ITD, *FLT3*-TKD, or both *FLT3*-ITD and -TKD mutations
- Among patients who received prior midostaurin or sorafenib in the ADMIRAL trial, survival was longer in patients treated with gilteritinib than in those treated with SC

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