The Benefit of Treatment with Quizartinib and Subsequent Bridging to HSCT for FLT3-ITD(+) Patients with AML

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Background

- FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) in acute myeloid leukemia (AML) is associated with early relapse after standard chemotherapy and poor survival
- The recommended strategy for treating patients with FLT3-ITD(+) AML who have relapsed or are refractory following chemotherapy is administration of additional chemotherapy followed by hematopoietic stem cell transplantation (HSCT) in responding patients because this offers the best option for long term survival
- However, the remission rate for relapsed/refractory FLT3-ITD(+) patients is only 20–30% with standard chemotherapy and this mutation is associated with significant morbidity and mortality. Therefore, a limited number of patients receive HSCT^{1,2}
- Quizartinib, an oral FLT3 inhibitor active against ITD mutant and wild-type FLT3, has shown promising activity in phase 1 and 2 studies³⁻⁵

Objectives

- To determine the activity of quizartinib monotherapy in patients aged \geq 18 years with FLT3-ITD(+) AML who are relapsed or have refractory disease after second line salvage therapy, or who relapsed after HSCT
- To examine the ability of quizartinib monotherapy to induce a remission that would allow patients to receive HSCT and determine the rate of bridge-to-HSCT and survival following HSCT

Methods

Study Design and Patients

- Two Phase 2 open-label, monotherapy studies
- Patients with morphologically documented AML and confirmation of FLT3-ITD status obtained by a central laboratory
- AC220-002

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- Cohort 2 (n=136): patients aged \geq 18 years and relapsed/refractory to second-line chemotherapy or HSCT
- Initial starting dose of quizartinib was 200 mg but reduced to 135 mg in males and 90 mg in females because of QTcF prolongation
- Subjects received starting dose of 200 mg (n=12), 135 mg (n=67), or 90 mg (n=57)
- 2689-CL-2004
- Same eligibility criteria as Cohort 2 AC220-002 study
- 76 subjects, randomized (males and females) to starting dose of quizartinib 30 mg/day (n=38) or quizartinib 60 mg/day (n=38)

Study Conduct

- Quizartinib administered once daily in continuous 28-day cycles until relapse, drug intolerance, or elective HSCT
- Dose escalation allowed if no CRc after 1 cycle or relapse
- Dose reduction required for Grade 2 or higher QTcF prolongation, prolonged myelosuppression or non-hematologic Grade 3 or 4 related AE
- Maintenance treatment with guizartinib was not allowed after HSCT
- After treatment discontinuation, patients were followed at 30 days for safety and every 3 months for survival and subsequent treatments
- Analysis based on data with a cutoff taken at 52 weeks following randomization of the last subject into the study. IWG response criteria for CRi and PR were modified and patients did not have to be transfusion independent. CR and CRp were according to IWG criteria

Table 1. Baseline Patient Characteristics

Median (range) age

Male sex, n (%)

Prior treatment and Relapsed, n (% Median duratio HSCT (CR1 or 0 Refractory to al

Prior MDS, n (%)

Cytogenetics,* n Favorable Intermediate Poor

ITD Burden, n (%) >50% >25%-50% >10%-25% Detectable (>0.3 Non-detectable Missing

Table 2. Patient Disposition

Discontinued stud Hematopoietic Disease progres Adverse events Death*

Other**

Median (range) time

Median (range) follo

+16/21 and 4/7 patients disc with quizartinib

patient choice (n=1)For 2689-CL-2004, other reasons included subject withdrawal (n=3) and randomized not treated (n=2).

Results

	Cohort 2 AC220-002 FLT3-ITD(+) (n=136)	2689-CL-2004 FLT3-ITD(+) (n=76)
e, years	50 (19–77)	55 (19–77)
	69 (51)	44 (58)
response on CR1, weeks CR2) , n (%) prior therapy, n (%)	94 (69) 22.0 41 (30) 42 (31)	53 (70) 26.1 21 (28) 22 (29)
	10 (7)	10 (13)
	68 0 54 (79) 14 (21)	60 2 (3) 51 (85) 7 (12)
3%—10%) (≤0.3%)	$\begin{array}{c} 46 & (34) \\ 62 & (46) \\ 28 & (21) \\ 0 \\ 0 \\ 0 \\ 0 \end{array}$	23 (30) 33 (43) 14 (18) 3 (4) 2 (3) 1 (1)

mplete remission following prior initial treatment; CR2=second complete remission following salvage treatment; HSCT=hematopoietic stem cell transplantation; MDS=myelodysplastic syndrome. vtogenetic data available for approximately 50% of patients; classification; per Grimwade D, et al. *Blood.* 2001;98(5):1312-1320.

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	AC220-002 FLT3-ITD(+) (n=136)	2689-CL-2004 FLT3-ITD(+) (n=76)		
treatment, n (%) stem cell transplantation ssion	135 (99) 47 (35) 56 (41) 21 (15) 5 (4) 6 (4)	75 (99) 26 (34) 35 (46) 7 (9) 2 (3) 5 (7)		
e on treatment, weeks	9.1 (0.3–108.1+)	10.0 (2.1, 52.0+)		
ow up, weeks	24.3 (0.7–109.1+)	19.4 (2.9, 77.4+)		
ontinued owing to AEs considered by investigator to be related to treatment with quizartinib. d lung infections) in AC220-002 were considered by investigator as possibly or probably related to treatment				

*2/5 deaths (hemorrhage and lung infections) in AC220-002 were considered by investigator as possibly or probably related to treatment **For AC220-002, other reasons included donor leukocyte infusion (n=2), patient noncompliance (n=2), physician decision (n=1), and

Table 3. Response and Survival Data

	Quizartinib Dose				
	AC220-002 Cohort 2			2689-CL-2004	
	90 mg/day (N=57)	135 mg/day (N=67)	200 mg/day (N=12)	30 mg/day (N=38)	60 mg/day (N=38)
CRc rate	47%	45%	42%	47%	47%
PR rate	25%	28%	50%	13%	24%
Median time to CRc (weeks)	4.3	4.1	4.1	4.4	4.6
Median OS in weeks (95% CI)	23.3 (19.9, 32.1)	24.1 (19.3, 29.9)	23.1 (15.0, 28.9)	20.9 (16.4, 31.0)	25.4 (16.3, 43.7)

Median baseline blast count was 81% for AC220-002 and 68% for 2689-CL-2004.

Table 4. Patient Characteristics for HSCT vs. No HSCT

	Protocol AC220-002 (N=136)		Protocol 2689-CL-2004 (N=76)	
	HSCT Post- Quizartinib (n=47)	No HSCT Post- Quizartinib (n=89)	HSCT Post- Quizartinib (n=28)	No HSCT Post- Quizartinib (n=48)
Median (range) age, years	46 (19–71)	52 (21–77)	51 (19–73)	57 (20–77)
Patients refractory to last therapy, n (%)	36 (77)	51 (57)	10 (36)	12 (25)
Median duration of CR1, weeks	22	22	15	26
Number (%) who received a prior HSCT	8 (17)	33 (37)	5 (18)	16 (33)
Median baseline bone marrow blast %	68%	84%	55%	72%
Best response to quizartinib, n(%) CRc PR NR	26 (55) 19 (40) 2 (4)	36 (40) 20 (22) 33 (37)	19 (68) 4 (14) 5 (18)	17 (35) 10 (21) 21 (44)

Figure 1. AC220-002 and 2689-CL-2004 (N=212)

Survival of FLT3-ITD(+) Patients by Response to Quizartinib and Subsequent HSCT or No HSCT

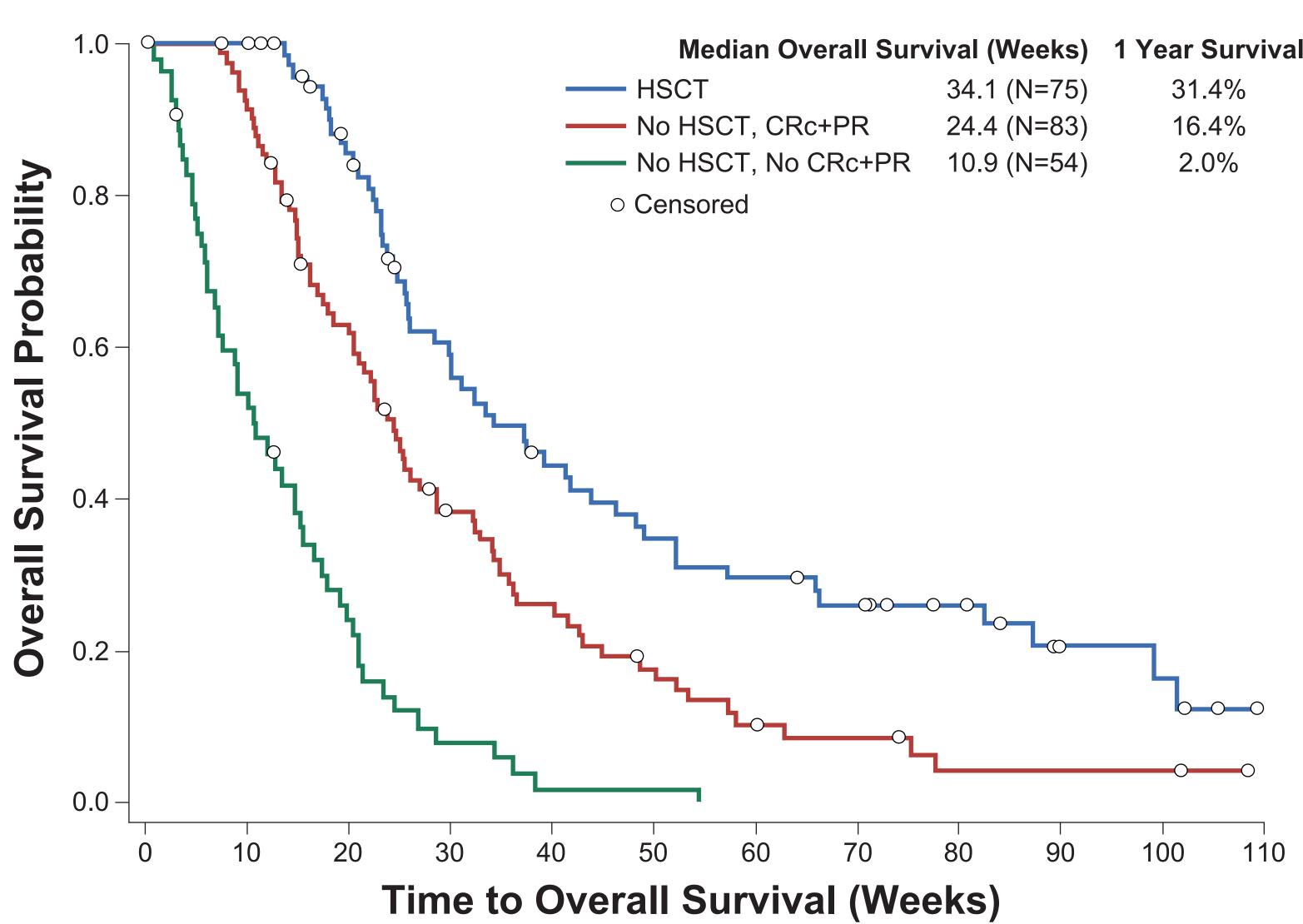


Table 5. Cause of Death Post-HSCT AC220-002 Study*

Cause of Death	N (%) (N=36)
AML Progression**	25 (69)
Infection	5 (14)
Transplant related	2 (6)
Unknown	2 (6)
Acute renal failure	1 (3)
Multi-organ failure	1 (3)

*Cause of death post-HSCT not collected in 2689-CL-2004 study. **Median time to death for AML progression is 22 weeks after ending treatment with quizartinib (minimum 9 weeks, maximum 93.7 weeks).

Long-term Survivors

- AC220-002 Cohort 2 and 2689-CL-2004
- 31/212 (15%) FLT3-ITD(+) patients remained alive for >12 months after taking quizartinib and were classified as "long-term survivors" (27 in AC220-002 and 4 in 2689-CL-2004)
- 29/31 (94%) long-term survivors achieved at least a PR (4 CR, 2 CRp, 14 CRi, and 9 PR) to quizartinib
- 19/31 (61%) went to HSCT immediately after receiving quizartinib, and their median treatment duration was 10 weeks



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eks)	1 Year Survival	
=75)	31.4%	
=83)	16.4%	
=54)	2.0%	

Summary

- The FLT3-ITD(+) patients in this analysis were all heavily pretreated (relapsed or refractory following salvage chemotherapy or HSCT), with median baseline blast counts of 81% (AC220-002) and 68% (2689-CL-2004).
- Approximately 45% of subjects in both studies achieved a reduction in bone marrow blast counts to less than 5% (CRc)
- 35% in study AC220-002 and 37% in study 2689-CL-2004 were successfully bridged immediately after quizartinib to a potentially curative HSCT
- 26% of patients who achieved a CRi with quizartinib and subsequently received HSCT are alive at >1 year, with multiple patients alive at >2 years

Conclusions

- A high percentage of heavily pretreated patients who had previously received salvage chemotherapy or HSCT achieved a response to quizartinib and were successfully bridged to transplant
- 25% (19/75) of subjects who received a transplant were alive at 1 year
- The most common cause of death after HSCT was AML progression and quizartinib maintenance therapy may decrease the relapse rate and increase median overall survival

Additional Studies

- A Phase 1, dose escalation study of quizartinib as post-transplant maintenance has completed enrollment
- A Phase 3 randomized study in adult relapsed or refractory FLT3-ITD(+) patients is currently recruiting with maintenance quizartinib post-HSCT

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