Efficacy and Safety of Quizartinib (AC220) in Patients Aged ≥70 Years With FLT3 ITD(+) or FLT3 ITD(–) Relapsed/Refractory Acute Myeloid Leukemia

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Background

- Advanced age and FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) in acute myeloid leukemia (AML) are each associated with early relapse after standard chemotherapy, and poor survival
- Quizartinib (AC220), an oral FLT3 inhibitor active against ITD mutant and wild-type FLT3, has shown promising activity in Phase 1 and 2 studies[1-3]

Objectives

- To determine the efficacy and safety of quizartinib monotherapy in patients aged ≥70 years with relapsed or refractory FLT3-ITD(+) and FLT3-ITD(–) AML

Methods

Study Design and Patients

- AC220-002: a Phase 2, open-label monotherapy study
- Patients with morphologically documented AML and confirmation of FLT3-ITD status obtained by a central laboratory
- Patients were enrolled into 2 cohorts
  - Cohort 1: patients ≥60 years and relapsed/refractory to first-line chemotherapy
  - Cohort 2: patients ≥18 years and relapsed/refractory to second-line chemotherapy or hematopoietic stem cell transplantation (HSCT)
- This analysis included 83 patients from both cohorts aged ≥70 years
  - 75 patients from Cohort 1
  - 8 patients from Cohort 2

Study Conduct

- Quizartinib once daily in continuous 28-day cycles until relapse, drug intolerance, or elective HSCT
- Quizartinib oral solution starting dose of 90–200 mg/day:
  - 200 mg/day for the first 17 patients enrolled
  - Dose reduced to 135 mg/day for male and 90 mg/day for female patients due to 35% of QTcF prolongation
- After treatment discontinuation, patients were followed at 30 days for safety and every 3 months for survival and subsequent treatments

Study Endpoints

- Primary
  - Complete remission (CR) rate
  - Composite CR rate (CRc): CR + CRp + CRi
    - CR
    - CR with incomplete platelet recovery (CRp: platelet count <100×10^9/L)
    - CR with incomplete hematologic recovery (CRi: absolute neutrophil count ≤10^9/L with or without platelet count <100×10^9/L); not required to be transfusion-independent
    - Partial remission (PR): criteria were the same as for CRi, except that the bone marrow blast count was between 5%–25% inclusive and represented a >50% decrease from baseline
    - Responses based on modified International Working Group criteria[4]
- Secondary
  - Duration of response
  - Overall survival

Results

Table 1. Baseline Characteristics

	FLT3-ITD(+) (n=60)	FLT3-ITD(–) (n=23)
Median (range) age, years	73 (70–86)	72 (70–78)
Male sex, n (%)	30 (50)	14 (61)
Prior treatment and response, n (%)		
Relapsed	37 (62)	12 (52)
Median duration CR1, weeks	29.0	25.5
Refractory to all prior therapy, n (%)	23 (38)	11 (48)
Prior MDS, n (%)	8 (13)	6 (26)
Cytogenetics,* n	34	10
Favorable	1 (3)	0
Intermediate	28 (83)	9 (90)
Poor	5 (15)	1 (10)
ITD allele burden, n (%)		
>50%	15 (25)	0
>25%–50%	34 (57)	0
>10%–25%	11 (18)	0
Detectable (>0.3%–10%)	0	6 (26)
Nondetectable (≤0.3%)	0	17 (74)

CR1=complete remission following previous initial treatment; FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication; MDS=myelodysplastic syndrome.
*Cytogenetic data were available for 57% of FLT3-ITD(+) patients and 43% of FLT3-ITD(–) patients. Per Grimwade D, et al. *Blood.* 2001;98(5):1312-1320.

Table 2. Prior Treatments

	FLT3-ITD(+) (n=60)	FLT3-ITD(–) (n=23)
Anthracyclines/mitroxantrone, n (%)	45 (75)	17 (74)
Daunorubicin	24 (40)	11 (48)
Idarubicin	18 (30)	4 (17)
Mitoxantrone	9 (15)	4 (17)
Other agents, n (%)		
Cytarabine	49 (82)	19 (83)
Etoposide	3 (5)	6 (26)
Fludarabine	1 (2)	1 (4)
Gemtuzumab ozogamicin	3 (5)	1 (4)
Azacitidine /decitabine	11 (18)	7 (30)

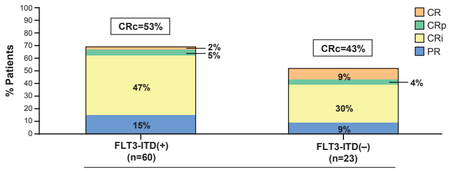
FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication.

Table 3. Patient Disposition

	FLT3-ITD(+) (n=60)	FLT3-ITD(–) (n=23)
Study treatment discontinued	59 (98)	23 (100)
Progressive disease	37 (62)	13 (57)
Elective bone marrow transplantation	2 (3)	2 (9)
Adverse events*	15 (25)	5 (22)
Death†	4 (7)	3 (13)
Other (withdrew consent)	1 (2)	0
Median duration of follow up (range), weeks	21.0 (1–93+)	19.0 (3.1–70.1+)
Median duration of quizartinib administration (range), weeks	14.6 (0.9–70.6+)	5.9 (1.1–41.4)

FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication.
*11/60 (18%) and 3/23 (13%) patients discontinued due to AEs considered by investigator to be related to treatment with quizartinib.
†3 deaths (sepsis, acute hepatic failure, and cerebral hemorrhage) were considered by the investigator as possibly or probably related to treatment with quizartinib.

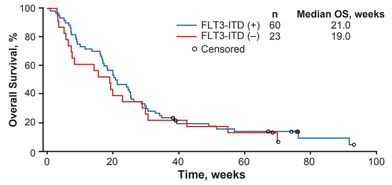
Figure 1. Response to Treatment



	FLT3-ITD(+)	FLT3-ITD(–)
Median (range) duration CRc, weeks	13.9 (0.1+–58.9)	9.3 (4.1–32.0+)
Median (range) time to CRc, weeks	5.2 (2.1–12.3)	8.1 (2.0–12.3)

CR=complete remission; CRc=composite complete remission; CRi=complete remission with incomplete hematologic recovery; CRp=complete remission with incomplete platelet recovery; FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication; PR=partial remission.
These results are consistent with previous reports.[1-3]

Figure 2. Overall Survival by FLT3-ITD Status



FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication; OS=overall survival.

Table 4. Characteristics of Patients (FLT3–ITD+ and ITD–) Surviving >1 Year

	Patients Who Survived >1 Year (n=12)
Median (range) age, years	72.5 (70–80)
Male sex, n (%)	9 (75)
Prior response	
Relapsed, n (%)	12 (100)
Median duration CR1, weeks	23.0
Prior MDS, n (%)	3 (25)
Cytogenetics,* n	10
Favorable	0
Intermediate	7 (70)
Poor	3 (30)
ITD allele burden, n (%)	
>50%	3 (25)
>25%–50%	4 (33)
>10%–25%	2 (17)
Detectable (0.3%–10%)	2 (17)
Nondetectable	1 (8)
Median duration of quizartinib administration (range), weeks	46.4 (5.1–70.6+)
Best response CRc, n (%)	9 (75)
Best response PR, n (%)	2 (17)

CR1=complete remission following previous initial treatment; FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication; HSCT=hematopoietic stem cell transplantation; MDS=myelodysplastic syndrome.
*Cytogenetic data were only collected for 50% of FLT3-ITD(+) patients and 56% of FLT3-ITD(–) patients.

Long-Term Survivors

- 13% (8/60) FLT3-ITD(+) patients remained alive for >12 months after taking quizartinib and were classified as long-term survivors
  - All 8 long-term survivors achieved at least a PR (2 CRp, 4 CRi, and 2 PR) to quizartinib and remained on treatment for a median of 53 weeks, with survival ranging from 56.9 to 93.0+ weeks
- Additionally, 17% (4/23) FLT3-ITD(–) patients were alive for >12 months, with 3 of the 4 achieving at least a PR (1 CR; 2 CRi) to quizartinib

Table 5. Grade 3 and 4 Treatment-Related AEs Reported in 5% ≥Patients*

AEs, n (%)	FLT3-ITD(+) (n=60)	FLT3-ITD(–) (n=23)	Overall (N=83)
Febrile neutropenia	11 (18)	7 (30)	18 (22)
Anemia	11 (18)	6 (26)	17 (20)
Electrocardiogram QTcF prolonged†	9 (15)	5 (22)	14 (17)
Thrombocytopenia	10 (17)	0 (0)	10 (12)
Fatigue	6 (10)	1 (4)	7 (8)
Platelet count decreased	1 (2)	5 (22)	6 (7)
Neutropenia	5 (8)	0 (0)	5 (6)
Pyrexia	4 (7)	0 (0)	4 (5)
White blood cell count decreased	2 (3)	2 (9)	4 (5)

AE=adverse event; FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication; QTcF=QT interval (Fridericia).
*The number of patients experiencing any grade 3 or 4 treatment-related AE was 48 (80%) in the FLT3-ITD(+) group, 15 (65%) in the FLT3-ITD(–) group, and 63 (76%) in the overall group.
†There have been no grade 4 QTcF prolongation events in this age group.

Table 6. QTcF Prolongation (N=83 Patients)

	200 mg (n=4)	135 mg (n=43)	90 mg (n=36)
Maximum post-baseline QTcF, n (%)			
>450 to ≤480 ms (grade 1)	1 (25)	13 (30)	12 (33)
>480 to ≤500 ms (grade 2)	1 (25)	12 (28)	9 (25)
>500 ms (grade 3 only)	2 (50)	8 (19)	10 (28)
Maximum change in post-baseline QTcF, n (%)			
≤30 ms	0	2 (5)	5 (14)
>30 to ≤60 ms	1 (25)	18 (42)	17 (47)
>60 ms	3 (75)	21 (49)	13 (36)

FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication; QTcF=QT interval (Fridericia).

Summary

- The patients in this analysis were all aged ≥70 years, with approximately 40% refractory to their last therapy, and therefore had a poor overall prognosis. Despite this:
  - There was a high response rate to quizartinib: CRc rate was 53% and 43%, and CR/CRp rate was 7% for FLT3-ITD(+) patients and 13% for FLT3-ITD(–) patients, respectively
  - Median survival was 21.0 and 19.0 weeks, with 13% and 17% surviving >1 yr for FLT3-ITD(+) and FLT3-ITD(–) patients, respectively
  - Quizartinib was generally well tolerated, with a 30 day mortality rate of 8%

Conclusions

- Elderly AML patients, particularly those aged ≥70 years, are more genetically heterogeneous than younger patients
- Our data show that patients aged ≥70 years with chemotherapy-resistant AML have response rates to FLT3 targeted therapy comparable to those observed in younger patients
- A Phase 3 study in adult relapsed or refractory FLT3-ITD(+) patients is planned to start in early 2014

References

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