Quizartinib (AC220) Produces High Response Rates and Long-Term Survival in Elderly Patients With FLT3-ITD(+) or FLT3-ITD(–) Relapsed/Refractory Acute Myeloid Leukemia

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7021

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
- Quizartinib, 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 activity of quizartinib monotherapy in patients aged ≥60 years with FLT3-ITD(+) and FLT3-ITD(–) AML who were relapsed or refractory after first-line therapy
- To examine the factors that affect long-term survival following quizartinib monotherapy

Methods

Study Design and Patients

- Phase 2, open-label monotherapy
- Patients with morphologically documented AML and confirmation of FLT3-ITD status obtained by a central laboratory
- Patients were enrolled into 2 cohorts
  - Cohort 1 (n=154): patients aged ≥60 years and relapsed/refractory to first-line chemotherapy
  - Cohort 2 (n=176): patients aged ≥18 years and relapsed/refractory to second-line chemotherapy or hematopoietic stem cell transplantation (HSCT)
- This analysis included 154 patients from Cohort 1 who had relapsed within <1 year or were refractory to first-line therapy

Study Conduct

- Quizartinib oral solution once daily in continuous 28-day cycles until relapse, drug intolerance, or elective HSCT
  - 200 mg /day for the first 17 patients enrolled, but this dose was reduced due to 35% grade 3 QTcF prolongation
  - All subsequent male patients received 135 mg/day; female patients received 90 mg/day.
- After treatment discontinuation, patients were followed up 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): same criteria as CR except for the presence of absolute neutrophil count ≤1.0 × 10^9/L or platelet count <100 × 10^9/L; patients with a CRi were 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 to treatment were based on modified International Working Group criteria[4]
- Duration of response
- Overall survival

Results

Table 1. Baseline Characteristics

	FLT3-ITD(+) (n=110)	FLT3-ITD(–) (n=44)
Median (range) age, years	69 (60–86)	69 (60–78)
Male sex, n (%)	55 (50)	21 (48)
Prior treatment and response		
Prior anthracycline/mitoxantrone, n (%)	87 (79)	34 (77)
Relapsed, n (%)	66 (60)	22 (50)
Median duration CR1, weeks	23.5	24.0
Refractory, n (%)	44 (40)	22 (50)
Prior MDS, n (%)	17 (15)	15 (34)
Cytogenetics,* n	62	23
Favorable	1 (2)	0
Intermediate	53 (85)	15 (65)
Poor	8 (13)	8 (35)
ITD allele burden, n (%)		
>50%	32 (29)	0
>25%–50%	53 (48)	0
>10%–25%	25 (22)	0
Detectable (>0.3%–10%)	0	10 (23)
Nondetectable (≤0.3%)	0	34 (77)

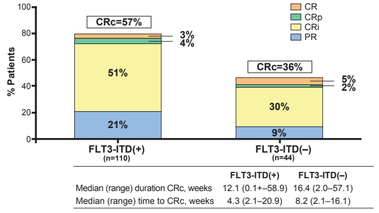
CR1=complete remission following previous initial treatment; FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication; HSCT=hematopoietic stem cell transplantation; MDS=myelodysplastic syndrome.
* Cytogenetic data were collected for 56% of FLT3-ITD(+) and 52% of FLT3-ITD(–) patients. Based on the modified International Working Group criteria.[4]

Table 2. Patient Disposition

	FLT3-ITD(+) (n=110)	FLT3-ITD(–) (n=44)
Study treatment discontinued, n (%)	108 (98)	44 (100)
Elective bone marrow transplantation	10 (9)	1 (2)
Progressive disease	65 (59)	29 (66)
Adverse events*	24 (22)	8 (18)
Death†	6 (5)	4 (9)
Other	3 (3)	2 (5)
Median duration of follow up (range), weeks	25.4 (0.4–96.0+)	19.1 (3.1–98.4)
Median duration of quizartinib treatment (range), weeks	14.1 (0.1–70.6+)	9.5 (1.1–77.0)

FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication.
*17/24 (71%) and 3/8 (38%) patients discontinued due to AEs considered by the investigator to be related to treatment with quizartinib.
†2/6 deaths (33%) and 1/4 death (25%), respectively, were considered by the investigator as possibly or probably related to treatment with quizartinib.

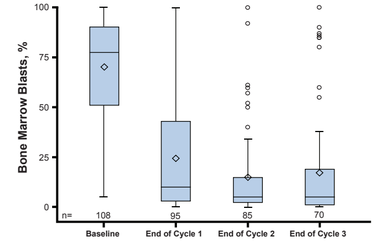
Figure 1. Response to Treatment



	FLT3-ITD(+)	FLT3-ITD(–)
Median (range) duration CRc, weeks	12.1 (0.1+–58.9)	16.4 (2.0–57.1)
Median (range) time to CRc, weeks	4.3 (2.1–20.9)	8.2 (2.1–16.1)

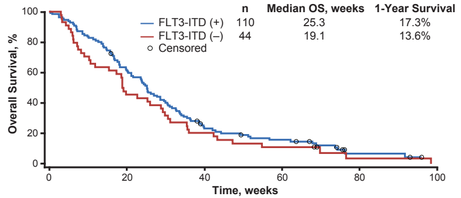
CR=complete remission; CRi=complete remission with incomplete hematologic recovery; CRp=complete remission with incomplete platelet recovery.

Figure 2. Quizartinib Causes a Rapid Decrease in Bone Marrow Blasts in FLT3-ITD(+) Patients



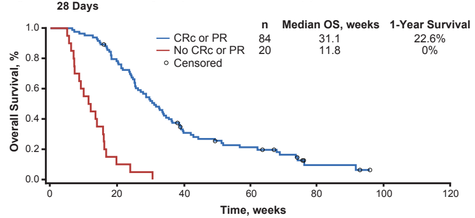
FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication
Box plots show medians (horizontal line in each box), 25th and 75th percentiles (upper and lower ends of each box), means (diamond in each box), 10th and 90th percentiles (bars), and individual outliers (circles).
Median BM blast % = 77.5% (baseline), 10% (cycle 1), and 4.9% (cycles 2 and 3).

Figure 3. Overall Survival by FLT3-ITD Status



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

Figure 4. Overall Survival by Response in 104 FLT3-ITD(+) Patients Who Lived at Least 28 Days



CRc=Composite complete remission; FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication; OS=overall survival; PR=partial remission.

Long-Term Survivors

- 15% (16/110) FLT3-ITD(+) patients remained alive for >12 months after taking quizartinib and were classified as long-term survivors
  - All long-term survivors achieved at least a PR (2 CR, 2 CRp, 8 CRi, and 4 PR) to quizartinib and remained on treatment for a median of 52.1 weeks, with survival from 56–96+ weeks
  - 1 of 16 long-term survivors underwent a HSCT after achieving a CRi
- Additionally, 14% (6/44) FLT3-ITD(–) patients were alive for >12 months, with 5 of the 6 achieving at least a PR (1 CR, 3 CRi, and 1 PR) to quizartinib

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

	Patients Who Survived >1 y (n=22)
Median (range) age, years	69.5 (65–80)
Male sex, n (%)	14 (64)
Prior response	
Relapsed, n (%)	9 (41)
Median duration CR1, weeks	34.0
Refractory to last prior therapy, n (%)	13 (59)
Prior MDS, n (%)	5 (23)
Cytogenetics,* n	11
Favorable	0
Intermediate	10 (91)
Poor	1 (9)
ITD allele burden, n (%)	
>50%	3 (14)
>25%–50%	7 (32)
>10%–25%	6 (27)
Detectable (0.3%–10%)	2 (9)
Nondetectable (≤0.3%)	4 (18)
Best response CRc, n (%)	16 (73)
Best response PR, n (%)	5 (23)
Median (range) duration of quizartinib administration, wk	46.4 (5.1–77.0)

CR1=complete remission following previous initial treatment; ITD=internal tandem duplication; MDS=myelodysplastic syndrome.
*Cytogenetics data were collected for 50% of FLT3-ITD(+) and 56% of FLT3-ITD(–) patients.

Table 5. Grade 3 or 4 Treatment-Related Adverse Events Occurring in ≥5% Patients*

Term, n (%)	FLT3-ITD(+) (n=110)	FLT3-ITD(–) (n=44)	Overall (N=154)
Anemia	28 (25)	8 (18)	36 (23)
Febrile neutropenia	24 (22)	8 (18)	32 (21)
Thrombocytopenia	21 (19)	6 (14)	27 (18)
Electrocardiogram QTcF prolonged†	11 (10)	5 (11)	16 (10)
Neutropenia	14 (13)	1 (2)	15 (10)
Leukopenia	11 (10)	2 (5)	13 (8)
Fatigue	7 (6)	1 (2)	8 (5)

FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication.
*The number of patients experiencing any grade 3 or 4 treatment-related AE was 83 (75%) in the FLT3-ITD(+) group, 28 (64%) in the FLT3-ITD(–) group, and 111 (72%) in the overall group.
†To date, there has been 1 grade 4 QTcF prolongation (torsade de pointes), which resolved after drug discontinuation.

Table 6. QTcF Prolongation (N=154 Patients)

	200 mg (n=5)	135 mg (n=74)	90 mg (n=75)
Maximum post-baseline QTcF, n (%)			
>450 to ≤480 ms (grade 1)	1 (20)	23 (31)	30 (40)
>480 to ≤500 ms (grade 2)	2 (40)	19 (26)	24 (32)
>500 ms* (grade 3/4)	1 (20)	11 (15)	13 (17)
Maximum change in post-baseline QTcF, n (%)			
≤30 ms	0	7 (9)	8 (11)
>30 to ≤60 ms	2 (40)	36 (49)	37 (49)
>60 ms	3 (60)	28 (38)	29 (39)

*To date, there has been 1 grade 4 QTcF prolongation (torsade de pointes), which resolved after drug discontinuation.

Summary

- The patients in this analysis were all aged ≥60 years; nearly 50% were refractory to their last therapy and the remainder had a short median duration of CR1, and therefore, had a poor overall prognosis. Despite this:
  - The CRc rate was 57% and 36% for FLT3-ITD(+) and FLT3-ITD(–) patients, respectively, with a CR/CRp rate of 7% for both
  - Median survival was 25.3 weeks for FLT3-ITD(+) patients and 19.1 weeks for FLT3-ITD(–) patients
- 22/154 (14%) of patients remained alive for >12 months after taking quizartinib and were classified as long-term survivors
  - 21 of the 22 (95%) long-term survivors achieved at least a PR to quizartinib, and the median duration of treatment was 52.1 weeks in the FLT3-ITD(+) patients
- Quizartinib was generally well tolerated, with a 30-day mortality rate of 6%

Conclusion

- These data for quizartinib show encouraging survival in a subset of elderly patients with relapsed/refractory FLT3-ITD(+) AML
- For patients who remained alive >1 year, the majority of whom were refractory or had a short CR1 duration, the long-term survival rate supports the clinical benefit of quizartinib
- A Phase 3 study in adult relapsed or refractory FLT3-ITD(+) patients is planned to start in early 2014

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