High Response Rate and Bridging to Hematopoietic Stem Cell Transplantation With Quizartinib (AC220) in Patients With FLT3-ITD Positive or Negative Relapsed/Refractory AML After Second-Line Chemotherapy or Previous Bone Marrow Transplant

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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, as 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 is associated with significant morbidity and mortality. Therefore, few patients receive a 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 studies[3-5]

Objectives

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

Methods

Study Design and Patients

- 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 (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 HSCT
- This analysis included the 176 patients from cohort 2

Study Conduct

- Quizartinib was administered once daily in continuous 28-day cycles until relapse, drug intolerance, or elective HSCT
- Quizartinib oral solution was provided at a starting dose of 90–200 mg/day:
  - 200 mg/day for the initial 17 patients enrolled, but 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:
  - Composite CR (CRc) rate
  - CR rate
    - Responses based on modified International Working Group criteria[6]
    - Complete remission (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
    - Composite CR (CRc): CR + CRp + CRi
    - 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
- Secondary:
  - Duration of response
  - Overall survival

Results

Table 1. Baseline Patient Characteristics

	FLT3-ITD(+) (n=136)	FLT3-ITD(–) (n=40)
Median (range) age, years	50 (19–77)	54 (23–73)
Male sex, n (%)	69 (51)	24 (60)
Prior treatment and response, n (%)		
Relapsed, n (%)	94 (69)	28 (70)
Median duration CR1, weeks	22.0	33.0
HSCT (CR1 or CR2), n (%)	41 (30)	12 (30)
Refractory to all prior therapy, n (%)	42 (31)	12 (30)
Prior MDS, n (%)	10 (7)	1 (3)
Cytogenetics,* n	68	21
Favorable	0	1 (5)
Intermediate	54 (79)	15 (71)
Poor	14 (21)	5 (24)
ITD Burden, n (%)		
>50%	46 (34)	0
>25%–50%	62 (46)	0
>10%–25%	28 (21)	0
Detectable (>0.3%–10%)†	0	14 (35)
Nondetectable (≤0.3%)	0	26 (65)

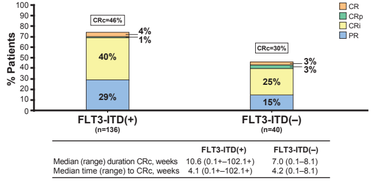
CR1=complete remission following prior initial treatment; CR2=second complete remission following salvage treatment; FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication; HSCT=hematopoietic stem cell transplantation; MDS=myelodysplastic syndrome.
*Cytogenetic data available for approximately 50% of patients; classification per Grimwade D, et al. *Blood*. 2001;98(5):1312-1320.
†0.3% was the lowest level FLT3-ITD detected.

Table 2. Patient Disposition

	FLT3-ITD(+) (n=136)	FLT3-ITD(–) (n=40)
Discontinued study treatment, n (%)	134* (99)	40 (100)
Elective hematopoietic stem cell transplantation	47 (35)	14 (35)
Disease progression	56 (41)	17 (43)
Adverse events†	21 (15)	3 (8)
Death‖	5 (4)	3 (8)
Other**	5 (4)	3 (8)
Median (range) time on treatment, weeks	9.1 (0.3–108.1+)	8.0 (1.0–38.1)
Median (range) follow up, weeks	24.3 (0.7–109.1+)	25.1 (4.1–95.6+)

FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication.
*2 patients continued to receive quizartinib at 101.6 weeks (complete remission) and 108.1 weeks (complete remission with incomplete platelet recovery), respectively.
†16/21 (76%) and 2/3 (67%) patients discontinued due to AEs considered by the investigator to be related to treatment with quizartinib.
‖2/5 deaths (40%) and 1/3 death (33%), respectively, were considered by the investigators as possibly or probably related to treatment with quizartinib.
**For FLT3-ITD(+) patients, other reasons were opted for donor leukocyte infusion (n=2), patient noncompliance (n=2), and patient choice (n=1); for FLT3-ITD(–) patients, other reason was patient choice (n=3).

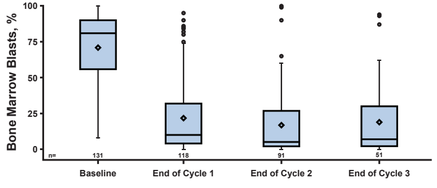
Figure 1. Best Response



	FLT3-ITD(+)	FLT3-ITD(–)
Median (range) duration CRc, weeks	10.6 (0.1+–102.1+)	7.0 (0.1–8.1)
Median time (range) to CRc, weeks	4.1 (0.1+–102.1+)	4.2 (0.1–8.1)

CI=confidence interval; CR=complete remission; CRc= composite CR (CR + CRp + CRi); 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.

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



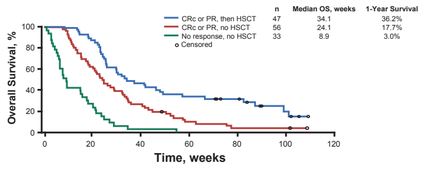
Box plots show medians (horizontal line in each box), 25th and 75th percentiles (upper and lower ends of each box), means (diamond in each box), 10th and 90th percentiles (bars), and individual outliers (circles). Median BM blast %=81% (baseline), 10% (cycle 1), 5% (cycle 2), and 7% (cycle 3).

Table 3. FLT3-ITD(+) Patient Characteristics by Subsequent HSCT Following Quizartinib

	HSCT Post-quizartinib (n=47)	No HSCT Post-quizartinib (n=89)
Median (range) age, years	46 (19–71)	52 (21–77)
Patients refractory to last therapy, n (%)	36 (77)	51 (57)
Median duration CR1, weeks	22	22
Number (%) who received a prior HSCT	8 (17)	33 (37)
Median baseline bone marrow blast %	68	84
Best Response to quizartinib, n (%)		
CRc	26 (55)	36 (40)
PR	19 (40)	20 (22)
NR	2 (4)	33 (37)

CRc=composite complete remission; FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication; HSCT=hematopoietic stem cell transplantation; NR=no response; PR=partial response.

Figure 3. Survival of FLT3-ITD(+) Patients by Response to Quizartinib and Subsequent HSCT or No HSCT



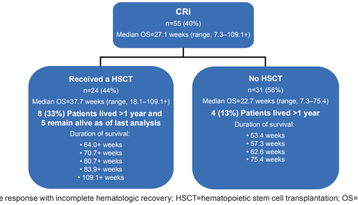
	n	Median OS, weeks	1-Year Survival
CRc or PR, then HSCT	47	34.1	36.2%
CRc or PR, no HSCT	56	24.1	17.7%
No response, no HSCT	33	8.9	3.0%

CRc=composite complete remission (CR + CRp + CRi); FLT3-ITD=FMS-like tyrosine kinase 3 internal tandem duplication; HSCT=hematopoietic stem cell transplantation; OS=overall survival; PR=partial remission.

Long-Term Survivors

- 27/136 (20%) FLT3-ITD(+) patients remained alive for >12 months after taking quizartinib and were classified as long term survivors
  - 26/27 long-term survivors achieved at least a PR (4 CR, 2 CRp, 12 CRi, 8 PR) to quizartinib
  - 17/27 went to HSCT immediately after receiving quizartinib, and their median treatment duration was 9.0 weeks
  - 10/27 did not undergo a HSCT after quizartinib, and their median treatment duration was 53.5 weeks

Figure 4. Clinical Benefit of Achieving a CRi With Quizartinib in FLT3-ITD(+) Patients



CRi=complete response with incomplete hematologic recovery; HSCT=hematopoietic stem cell transplantation; OS=overall survival.

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

Dictionary-Derived Term, n (%)	FLT3-ITD(+) (n=136)	FLT3-ITD(–) (n=40)	Overall (N=176)
Febrile neutropenia	35 (26)	8 (20)	43 (24)
Anemia	27 (20)	12 (30)	39 (22)
Thrombocytopenia	22 (16)	2 (5)	24 (14)
Neutropenia	18 (13)	1 (3)	19 (11)
Electrocardiogram QTcF prolonged†	15 (11)	1 (3)	16 (9)
Leukopenia	13 (10)	1 (3)	14 (8)
Pneumonia	5 (4)	5 (13)	10 (6)
Alanine aminotransferase increased	6 (4)	2 (5)	8 (5)
Platelet count decreased	6 (4)	2 (5)	8 (5)

QTcF=QT interval.
*The number of patients experiencing any grade 3 or 4 treatment-related AE was 88 (65%) in the FLT3-ITD(+) group, 23 (58%) in the FLT3-ITD(–) group, and 111 (63%) in the overall group.
†No grade 4 QTcF prolongation events.

Table 5. QTcF Prolongation (N=176)

	200 mg (n=12)	135 mg (n=91)	90 mg (n=73)
Maximum postbaseline QTcF, n (%)			
>450 to ≤480 ms (grade 1)	3 (25)	40 (44)	31 (42)
>480 to ≤500 ms (grade 2)	4 (33)	15 (16)	14 (19)
>500 ms (all grade 3)	5 (42)	14 (15)	12 (16)
Maximum change in post-baseline QTcF, n (%)			
≤30 ms	0	11 (12)	5 (7)
>30 to ≤60 ms	1 (8)	45 (49)	36 (49)
>60 ms	11 (92)	34 (37)	31 (42)

QTcF=QT interval.
*No grade 4 QTcF prolongation events.

Summary

- The FLT3-ITD(+) patients in this analysis were all heavily pretreated (relapsed or refractory following salvage chemotherapy or HSCT); the median baseline blast count was 81%. Despite this:
  - The CRc rate was 46% and 30% with a CR/CRp rate of 5% in FLT3-ITD(+) and 6% and FLT3(–) patients, respectively
  - 35% of patients were successfully bridged immediately after quizartinib to a potentially curative HSCT, with the greatest proportion receiving a HSCT after achieving a CRi with quizartinib
  - 33% of patients who achieved a CRi with quizartinib and subsequently received a HSCT are alive >1 year, with multiple patients alive >2 years

Conclusions

- A high percentage of heavily pretreated patients who had previously received salvage chemotherapy or HSCT achieved a response to quizartinib
- Achieving a response to quizartinib (primarily CRi) is clinically meaningful for these patients, given the positive impact on overall survival
- Given the limited treatment options for these patients, the long-term survivor rate supports the clinical benefit of quizartinib
- Quizartinib was generally well tolerated, with manageable toxicity
  - The incidence of grade 3 QTcF prolongation was 18%; there were no grade 4 QTcF prolongation events
- A Phase 3 randomized study in adult relapsed or refractory FLT3-ITD(+) patients is planned to start early in 2014

References

1. Levis M, et al. *Blood*. 2011;117(12):3294-3301.
2. Forman SJ and Rowe JM. *Blood*. 2013;121(7):1077-1082.
3. Cortes JE, et al. *Journal of Clinical Oncology*. In press.
4. Cortes JE, et al. *Blood*. 2012;12:48.
5. Levis MJ, et al. *Blood*. 2012;120:673 [abstract].
6. Cheson BD, et al. *J Clin Oncol*. 2003;21(24):4642-4649.

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