# Treatment With Quizartinib (AC220) Enables a High Rate of Patients With Relapsed or Refractory FLT3-ITD(+) Acute Myeloid Leukemia to be Bridged to HSCT

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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 studies[3-5]

## Objectives

- To determine the activity of quizartinib monotherapy in patients aged ≥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
  - Cohort 2 (n=136): patients aged ≥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 quizartinib 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

## Results

### Table 1. Baseline Patient Characteristics

| | Cohort 2 AC220-002 FLT3-ITD(+) (n=136) | 2689-CL-2004 FLT3-ITD(+) (n=76) |
|---|---|---|
| Median (range) age, years | 50 (19–77) | 55 (19–77) |
| Male sex, n (%) | 69 (51) | 44 (58) |
| Prior treatment and response | | |
| Relapsed, n (%) | 94 (69) | 53 (70) |
| Median duration CR1, weeks | 22.0 | 26.1 |
| HSCT (CR1 or CR2) , n (%) | 41 (30) | 21 (28) |
| Refractory to all prior therapy, n (%) | 42 (31) | 22 (29) |
| Prior MDS, n (%) | 10 (7) | 10 (13) |
| Cytogenetics,* n | 68 | 60 |
| Favorable | 0 | 2 (3) |
| Intermediate | 54 (79) | 51 (85) |
| Poor | 14 (21) | 7 (12) |
| ITD Burden, n (%) | | |
| >50% | 46 (34) | 23 (30) |
| >25%–50% | 62 (46) | 33 (43) |
| >10%–25% | 28 (21) | 14 (18) |
| Detectable (>0.3%–10%) | 0 | 3 (4) |
| Non-detectable (≤0.3%) | 0 | 2 (3) |
| Missing | 0 | 1 (1) |

CR1=complete remission following prior initial treatment; CR2=second complete remission following salvage treatment; 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.

### Table 2. Patient Disposition

| | AC220-002 FLT3-ITD(+) (n=136) | 2689-CL-2004 FLT3-ITD(+) (n=76) |
|---|---|---|
| Discontinued study treatment, n (%) | 135 (99) | 75 (99) |
| Hematopoietic stem cell transplantation | 47 (35) | 26 (34) |
| Disease progression | 56 (41) | 35 (46) |
| Adverse events† | 21 (15) | 7 (9) |
| Death* | 5 (4) | 2 (3) |
| Other** | 6 (4) | 5 (7) |
| Median (range) time on treatment, weeks | 9.1 (0.3–108.1+) | 10.0 (2.1, 52.0+) |
| Median (range) follow up, weeks | 24.3 (0.7–109.1+) | 19.4 (2.9, 77.4+) |

†16/21 and 4/7 patients discontinued owing to AEs considered by investigator to be related to treatment with quizartinib.
*2/5 deaths (hemorrhage and lung infections) in AC220-002 were considered by investigator as possibly or probably related to treatment with quizartinib.
**For AC220-002, other reasons included donor leukocyte infusion (n=2), patient noncompliance (n=2), physician decision (n=1), and patient choice (n=1).
For 2689-CL-2004, other reasons included subject withdrawal (n=3) and randomized not treated (n=2).

### 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) |

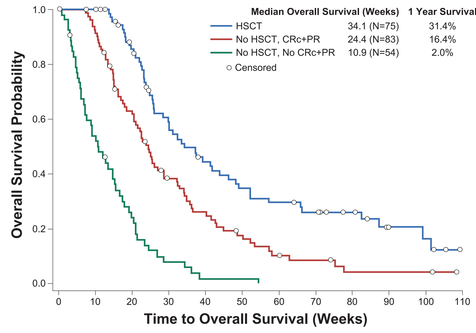
Median baseline blast count was 81% for AC220-002 and 68% for 2689-CL-2004.

### 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 R1, 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 | 26 (55) | 36 (40) | 19 (68) | 17 (35) |
| PR | 19 (40) | 20 (22) | 4 (14) | 10 (21) |
| NR | 2 (4) | 33 (37) | 5 (18) | 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

## 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

## References

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