Quizartinib (AC220) in Patients With FLT3-ITD(+) Relapsed or Refractory Acute Myeloid Leukemia: Final Results of a Randomized Phase 2 Study

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Background

- FLT3-ITD in AML is associated with early relapse and poor survival after treatment with standard chemotherapy
- Quizartinib is an orally active FLT3-ITD inhibitor
- A previous Phase 2 study included subjects with FLT3-ITD(+) AML, relapsed/refractory to 2nd line chemotherapy or relapsed after hematopoietic stem cell transplant (HSCT), doses of 90, 135 or 200 mg/day
  - 46% of subjects achieved CRc (CRc = CR + CRp + CRi)
  - 35% of subjects were bridged to HSCT (mostly after achieving CRi)
  - 33% of subjects with a CRi and bridged to HSCT were alive beyond 1 year
  - Quizartinib was generally well tolerated
    - Grade 3 QTcF was observed in 18% of subjects
    - No Grade 4 QTcF prolongation was recorded

Study Design and Population

- This was an open label, randomized comparison of two doses of quizartinib, 30 mg/day and 60 mg/day, given for 28 day continuous cycles, to FLT3-ITD(+) subjects who were ≥18yrs and were relapsed or refractory to salvage therapy or relapsed after HSCT
- Subjects had their dose reduced for any of the following reasons:
  - Grade 2 or higher QTcF prolongation
  - Grade 3 or higher related non-hematologic toxicity
  - Myelosuppression for subjects in CRc
- Subjects could have their dose increased for lack of CRc after 1 cycle or loss of response
- The primary endpoints were:
  - CRc Rate (CRc = CR + CRp + CRi)
  - Incidence of ≥ Grade 2 QTcF Prolongation
- The secondary endpoints included:
  - Overall Survival
  - Duration of Response
  - Bridge to Transplant Rate
  - Safety
- 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 subjects did not have to be transfusion independent. CR and CRp were according to IWG Criteria

Table 1. Patient Characteristics

	N (%) or Median [range]		
	30 mg/day (N=38)	60 mg/day (N=38)	Total (N=76)
Age (years)	57 [19-77]	53 [20-74]	55 [19-77]
Age ≥60 years	16 (42)	10 (26)	26 (35)
Males	22 (58)	22 (58)	44 (58)
ECOG PS 2	7 (18)	5 (14)	12 (16)
Secondary AML	3 (8)	7 (18)	10 (13)
FLT3-ITD(+) allelic ratio	35 (92)	35 (92)	70 (92)
>10% and ≤25%	9 (24)	5 (13)	14 (18)
≥25% and ≤50%	20 (53)	13 (34)	33 (43)
>50%	6 (16)	17 (45)	23 (30)
Intermediate Cytogenetic Risk*	26 (68)	25 (66)	51 (67)
Poor Cytogenetic Risk*	4 (11)	3 (8)	7 (9)

*Cytogenetic information based on available data

Table 2. Prior Treatment and Response

	30 mg/day (N=38)	60 mg/day (N=38)	Total (N=76)
Refractory N (%)	9 (24)	13 (34)	22 (29)
Relapsed N (%)	29 (76)	24 (63)	53 (70)
CR1 (weeks) Median [range]	17.4 [2.1, 60.9]	26.1 [3.6, 78.3]	26.1
Previous HSCT N (%)	9 (24)	12 (32)	21 (28)
Median time from previous HSCT (weeks)	23.6	28.1	-
Prior FLT3 Therapy N (%)	5 (13)	7 (18)	12 (16)
Median time from end of prior FLT3 therapy to start of quizartinib treatment (weeks)	4.9	13.3	-

All 12 subjects taking a prior FLT3 therapy received sorafenib. 1 also received midostaurin and 1 also received crenolanib

Table 3. Patient Disposition

	30 mg/day (N=38)	60 mg/day (N=38)	Total (N=76)
Active treatment	0	1 (3)	1 (1)
Discontinued	38 (100)	37 (97)	75 (99)
Relapse / Lack of Efficacy	19 (50)	16 (42)	35 (46)
HSCT	11 (29)	15 (39)	26 (34)
Adverse event(s)*	6 (16)	1 (3)	7 (9)
Subject withdrawal	1 (3)	2 (5)	3 (4)
Randomized no tx	0	2 (5)	2 (3)
Death**	1 (3)	1 (3)	2 (3)

*3 of 7 AEs leading to discontinuation were related to study drug and all were in the 30 mg/day group: neutropenic sepsis, diarrhea, and pleural effusion. The last 2 events occurred after the subject had escalated to 60 mg/day
**2 deaths, one due to AML progression and one due to sepsis, disseminated intravascular coagulation + multi-organ failure – both considered unrelated to quizartinib

Table 4. Quizartinib Treatment Duration and Dose Modifications*

	Median [range] or N (%)		
	30 mg/day (N=38)	60 mg/day (N=36**)	Total (N=74)
Median Duration of Treatment (range), weeks	9.4 [2.1, 33.4]	10.2 [2.6, 52+]	
Dose Interrupted	14 (37)	17 (47)	31 (42)
Dose Reduced	12 (32)	11 (31)	23 (31)
QTc prolongation	1	2	3
Other adverse events	2	2	4
Myelosuppression	4	6	10
Dose Escalated	24 (63)	7 (19)	31 (42)
No response	11	2	13
Loss of response	13	5	18

*At the time of last dose, 5 patients were receiving 20 mg/day, 22 patients were receiving 30 mg/day, 42 patients were receiving 60 mg/day and 5 patients were receiving 90 mg/day
**Two patients were randomized but did not receive drug due to ineligibility

Table 5. Treatment-Emergent AEs: Incidence ≥25%

	N (%)			
	30 mg/day (N=38)		60 mg/day (N=36)	
Adverse Event	All grades	Grade 3/4	All grades	Grade 3/4
Any event	37 (97)	30 (79)	36 (100)	32 (89)
Anemia	18 (47)	14 (37)	9 (25)	6 (17)
Fatigue	13 (34)	1 (3)	8 (22)	2 (6)
Pyrexia	11 (29)	3 (8)	13 (36)	3 (8)
Vomiting	11 (29)	0	13 (36)	3 (8)
Febrile neutropenia	11 (29)	11 (29)	13 (36)	13 (36)
Diarrhea	10 (26)	1 (3)	13 (36)	1 (3)
Cough	9 (24)	1 (3)	9 (25)	0
Nausea	9 (24)	0	17 (47)	3 (8)
Abdominal Pain	6 (16)	0	11 (31)	0
Headache	4 (11)	1 (3)	9 (25)	1 (3)

Table 6. Overall Response

	N (%)		
Best Response	30 mg/day* (N=38)	60 mg/day* (N=38)	Total (N=76)
CRc (CR+CRp+CRi)	18 (47)	18 (47)	36 (47)
CR	2 (5)	1 (3)	3 (4)
CRp	0	1 (3)	1 (1)
CRi	16 (42)	16 (42)	32 (42)
PR	5 (13)	9 (24)	14 (18)
Duration of CRc* weeks [95% CI]	4.1 [3.9, 9.7]	20.0 [4.3, 20]	5.3 [4.1, 12.3]

*30 mg/day arm: 7/18 censored; 5 censored due to HSCT
60 mg/day arm: 11/18 censored; 9 censored due to HSCT

Figure 1. Overall Survival by Dose

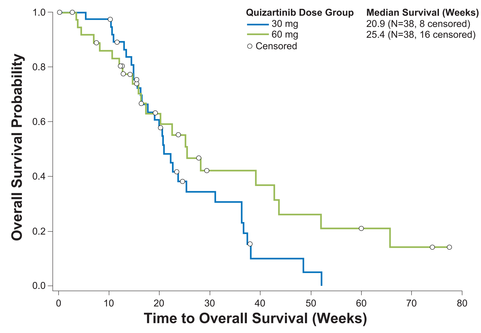

Figure 2. Overall Survival by Dose and HSCT Post-Quizartinib

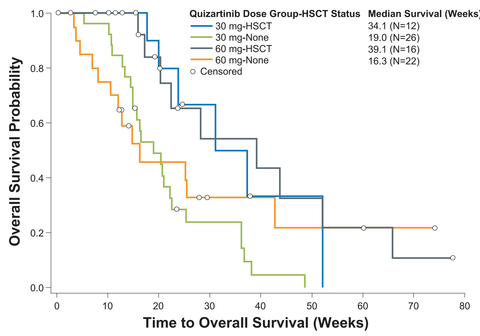

Table 7. Updated Results: Bridge to Transplant

	N (%)	
	30 mg/day (N=38)	60 mg/day (N=38)
Bridge to Transplant Rate	12 (32)	16 (42)*
CR	2 (5)	1 (3)
CRi	7 (18)	9 (24)
PR	1 (3)	3 (8)
NR	2 (5)	3 (8)
Median Survival (weeks)	34.1	39.1
Alive	6 (50)	7 (44)
Died	6 (50)	9 (56)

*2 subjects went to HSCT but listed progressive disease and adverse event as the reasons for treatment discontinuation

Long-term Survivors

- 24 subjects were alive at >24 weeks and 35 had died (17 were censored before 24 weeks)
- 4 subjects remained alive >12 months and 51 had died (21 censored before 1 year follow up). These 4 subjects were classified as "long-term survivors"
  - 3/4 long-term survivors achieved at least a PR (2 CRi and 1 PR) to quizartinib
    - 2/4 (50%) long-term survivors went to HSCT after receiving quizartinib and were on quizartinib for 10 and 14.6 weeks
    - 1/4 (25%) long-term survivors remain on study taking quizartinib for over 1 year

Table 8. Comparison of Quizartinib Doses in Two Phase 2 Studies in >200 Subjects

	2689-CL-2004		AC220-002 (Cohort 2)		
	30 mg/day (N=38)	60 mg/day (N=38)	90 mg/day (N=57)	135 mg/day (N=67)	200 mg/day (N=12)
Best Response					
CRc Rate	47%	47%	47%	45%	42%
PR Rate	13%	24%	25%	28%	50%
Maximum value of QTcF (msec)					
>450 to ≤480	42%	47%	35%	48%	25%
>480 to ≤500	5%	14%	21%	13%	33%
>500	5%	3%	21%	15%	42%
Maximum change in QTcF from baseline (msec)					
≤30	50%	44%	9%	9%	0%
>30 to ≤60	47%	36%	46%	51%	8%
>60	3%	19%	46%	39%	92%

Summary

- Quizartinib at doses of 30 and 60 mg daily, in second salvage or post HSCT in FLT3-ITD(+) AML subjects, demonstrated a high degree of activity (CRc 47%) equivalent to higher daily doses (90, 135 and 200 mg) administered in the previous Phase 2 study
- Bridge to transplant rate was equivalent to that at higher doses; improved median survival for HSCT subjects in updated data
- Overall survival was equivalent to previous Phase 2 study at higher doses
- There was a decrease in QTcF prolongation at lower doses together with an acceptable safety profile

Further Studies

- A Phase 3 study comparing the effect on overall survival of either quizartinib (starting dose of 30 mg/day) or standard chemotherapy in subjects with relapsed/refractory FLT3-ITD AML is underway

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