Results Of a Phase 2 Randomized, Open-Label, Study of Lower Doses of Quizartinib (AC220; ASP2689) In Subjects With FLT3-ITD Positive Relapsed or Refractory Acute Myeloid Leukemia (AML)

J. E. Cortes[1], M. S. Tallman[2], G. Schiller[3], D. Trone[4], G. Gammon[4], S. Goldberg[5], A. E. Perl[6], J-P. Marie[7], G. Martinelli[8], M. J. Levis[9]

[1]The University of Texas M. D. Anderson Cancer Center, Houston, TX [2]Memorial Sloan-Kettering Cancer Center, New York, NY [3]UCLA School of Medicine, Los Angeles, CA [4]Ambit Biosciences Corporation, San Diego, CA [5]Hackensack University Medical Center, Hackensack, NJ [6]University of Pennsylvania, Philadelphia, PA [7]Saint-Antoine Hospital, Paris, France [8]University of Bologna, Bologna, Italy [9]Johns Hopkins University School of Medicine, Baltimore, MD

Lower Dose Quizartinib Background

- FLT3-ITD in AML associated with poor outcome
- Quizartinib, an oral FLT3 inhibitor, with clinical activity in a Phase 2 Study in 333 subjects
- Phase 2: 176 patients age ≥18 years with AML relapsed/refractory to 2nd-line chemotherapy or HSCT
  - CRc 46% among 136 FLT3-ITD(+)
  - 35% bridged to HSCT (most after achieving a CRi)
  - 33% who achieved a CRi and then HSCT alive >1 year
  - Generally well tolerated
    - Grade 3 QTcF prolongation 18%; no Grade 4 QTcF prolongation
- To improve the benefit:risk profile of quizartinib lower doses were studied in this follow-on Phase 2b Study

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Lower Dose Quizartinib Study Design

- **Eligibility**
  - **≥ 18 yrs**
  - **Primary AML or secondary to MDS**
  - **FLT3-ITD(+) by central laboratory**
  - **Relapsed after, or refractory to 1 line of salvage therapy or relapsed after HSCT**
- **Randomized to 30 mg or 60 mg continuous daily dosing**
- **Dose reduction**
  - **Grade 2 or higher QTcF prolongation**
  - **Grade 3 or higher related non-hematologic toxicity**
  - **Myelosuppression for subjects in CRc**
- **Dose increase for lack of CRc after 1 cycle or loss of response**
- **76 patients enrolled from May 21, 2012 to March 27, 2013**

Lower Dose Quizartinib Study Endpoints

- **Primary Endpoints:**
  - **CRc Rate (CRc = CR + CRp + CRi)**
  - **Incidence of ≥ Grade 2 QTcF Prolongation**
- **Secondary Endpoints include:**
  - **Overall Survival**
  - **Duration of Response**
  - **Bridge to Transplant Rate**
  - **Safety**
- **Preliminary Analysis based on data available until May 28, 2013 with a minimum of 8 weeks of follow-up since last subject first visit**

Lower Dose Quizartinib Patient Characteristics

	No. (%), 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)

Patients enrolled in North America (76%) and European Union (24%)

Lower Dose Quizartinib Patient Characteristics

	No. (%), or Median [range]		
	30 mg/day (N = 38)	60 mg/day (N = 38)	Total (N = 76)
FLT3-ITD (+)	35 (92)	35 (92)	70 (92)
≥ 25% and ≤50%	20 (53)	13 (34)	33 (43)
> 50%	6 (16)	17 (45)	23 (30)
Intermediate/Poor Cytogenetic Risk	30/30 (100)	28/30 (93)	58/60 (97)

Lower Dose Quizartinib
Prior Treatment and Response

	No. (%), or Median [range]		
	30 mg/day (N = 38)	60 mg/day (N = 38)	Total (N = 76)
Relapsed	29 (76)	24 (63)	53 (70)
Duration of CR1 (weeks)	17.4	26.1	26.1
Refractory	9 (24)	13 (34)	22 (29)
Previous HSCT	9 (24)	12 (32)	21 (28)
Prior FLT3 Therapy	5 (13)	7 (18)	12 (16)

Lower Dose Quizartinib
Initial Results: Treatment Summary

	Median [range]		
	30 mg/day (N=38)	60 mg/day (N=36)*	Total (N=74)
Length of treatment (weeks)	9.4 [2.1, 24.9+]	10.3 [2.6, 26.0]	10.0 [2.1, 26.0]
	(2 still on treatment)	(2 still on treatment)	
Length of follow-up from 1st dose (weeks)	17.1 [5.3, 38.1]	16.3 [0.1, 42.7]	16.4 [0.1, 42.7]
	(16 continue to be followed)	(19 continue to be followed)	

* 2 subjects were randomized, but not treated.

Lower Dose Quizartinib
Initial Results: Dose Modifications

	No. (%)		
	30 mg/day (N = 38)	60 mg/day (N = 36)	Total (N = 74)
Dose Interrupted	14 (37)	17 (47)	31 (42)
Dose Reduced	9 (24)*	10 (28)	19 (26)*
QTc prolongation	1	2	3
Other adverse events	1	2	3
Myelosuppression	5	6	11
Dose Escalated	24 (63)	7 (19)	31 (42)
No response	11	2	13
Loss of response	13	5	18

*2 patients with incomplete data

Lower Dose Quizartinib
Initial Results: Patient Disposition

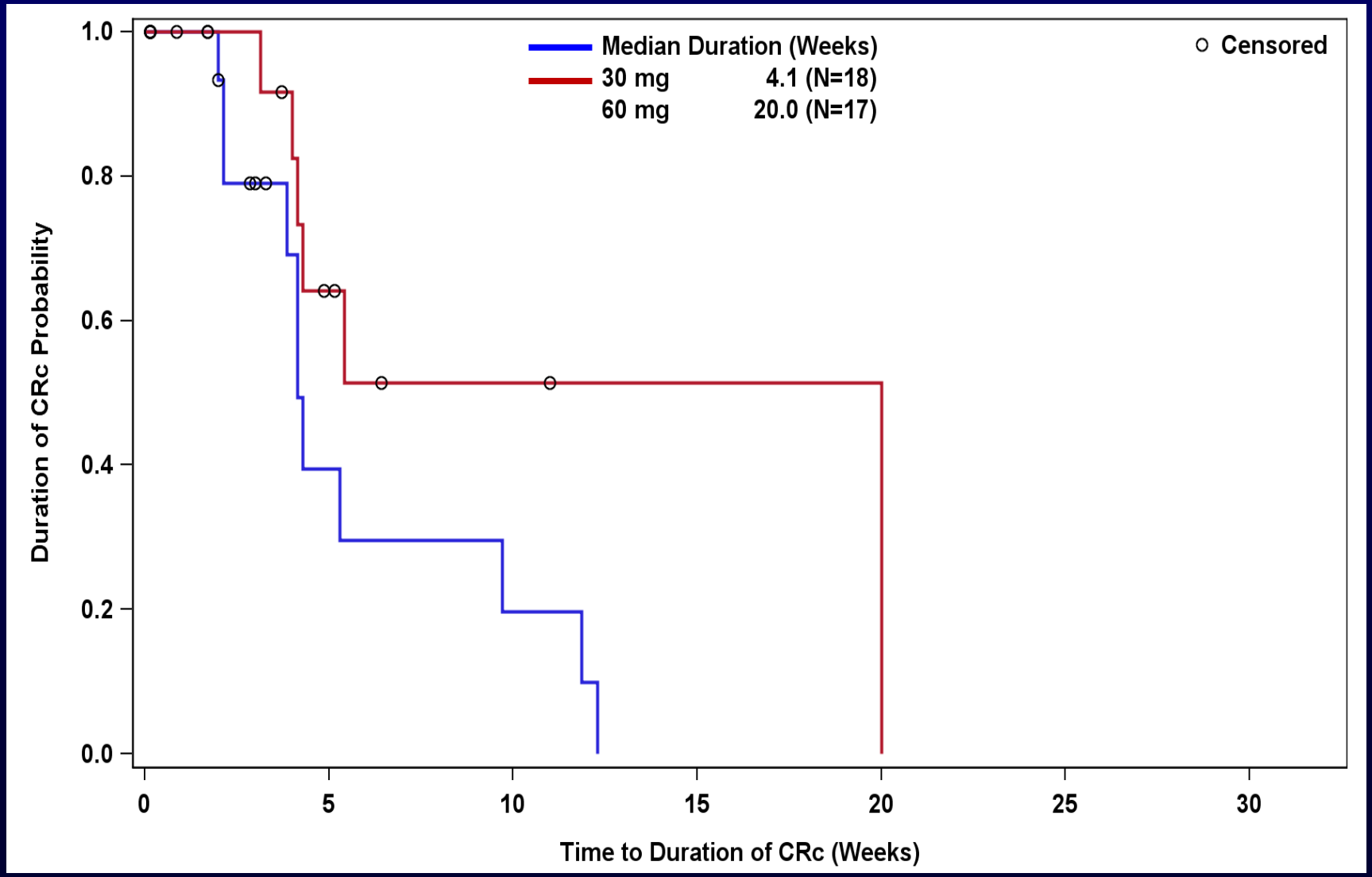
	No. (%)		
	30 mg/day (N = 38)	60 mg/day (N = 38)	Total* (N = 76)
Active treatment	2 (5)	2 (5)	4 (5)
Discontinued	36 (95)	36 (95)	72 (95)
Relapse / Lack of Efficacy	17 (45)	15 (39)	32 (42)
HSCT*	11 (29)	15 (40)	26 (34)
Adverse event(s)	6 (16)	1 (3)	7 (9)
Subject withdrawal	1 (3)	2 (5)	3 (4)
Randomized no tx	0	2 (5)	2 (3)
Death	1 (3)	1 (3)	2 (3)

* 2 additional subjects went to HSCT but listed progressive disease and adverse event as reason for treatment discontinuation.

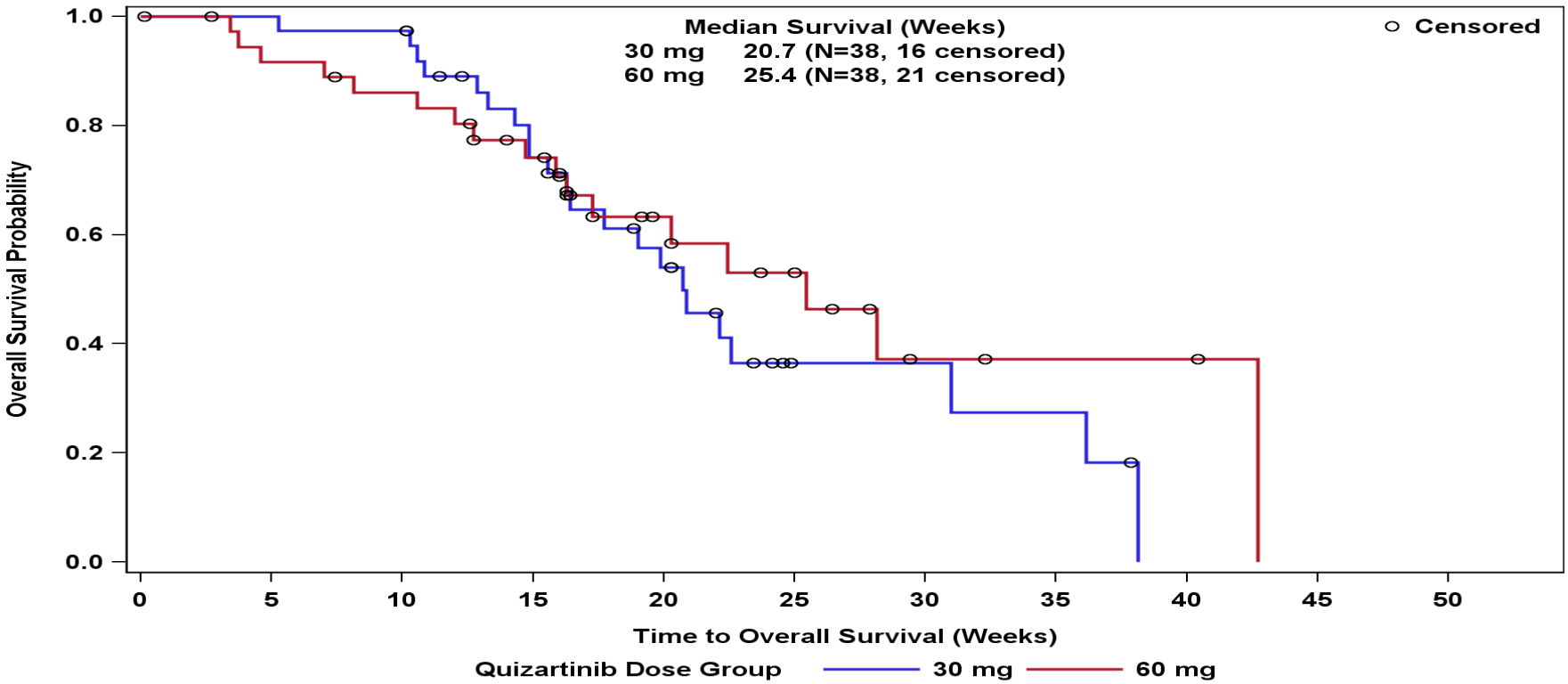
Lower Dose Quizartinib Initial Results: Overall Response

Best Response	No. (%) 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)
CRc+PR	23 (61)	27 (71)	50 (66)
PR	5 (13)	9 (24)	14 (18)

Lower Dose Quizartinib
Initial Results: Duration of CRc by Dose



Lower Dose Quizartinib Initial Results: Overall Survival by Dose



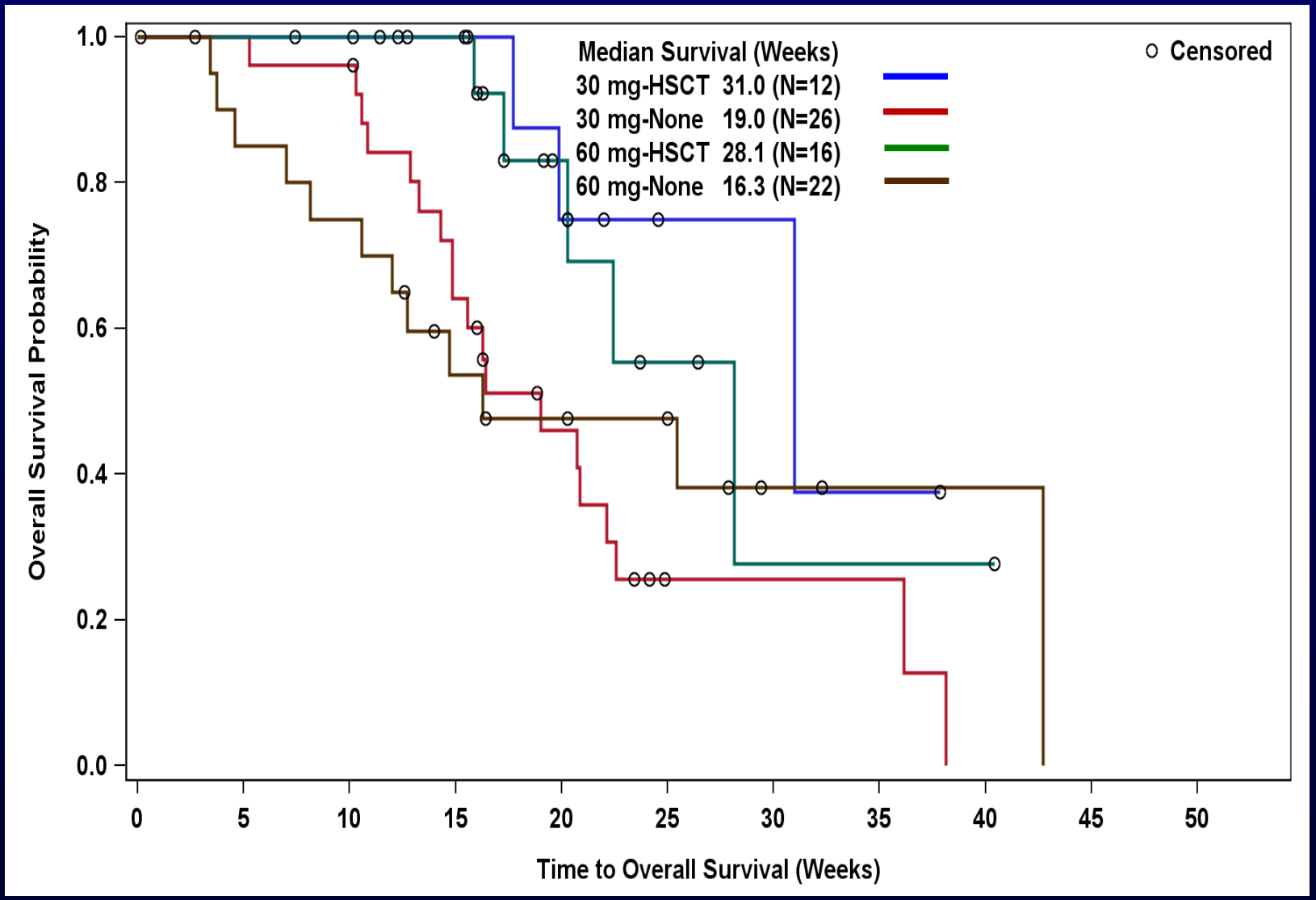
- Thirty-seven subjects (49%) remain censored for overall survival (2 randomized but not treated; and 35 subjects remain alive).
- Of the 35 subjects who remain alive (range: 7.4 – 40.4+), there are 10 subjects alive >24 weeks and 2 alive >36 weeks (37.9+ weeks, and 40.4+ weeks).

Lower Dose Quizartinib
Initial Results: Bridge to Transplant

	No. (%)	
	30 mg/day (N = 38)	60 mg/day (N = 38)
Bridge to Transplant Rate	12 (32)	16 (42)*
Median Survival (weeks)	31.0	28.1
Alive	9 (75)	11 (69)
Died	3 (25)	5 (31)

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

Lower Dose Quizartinib
Initial Results: Overall Survival by Dose ± HSCT



Lower Dose Quizartinib Initial Results: Treatment-Emergent AEs: Incidence ≥25%

	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)	33 (92)
Anemia	18 (47)	14 (39)	8 (22)	6 (8)
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	10 (26)	10 (26)	13 (36)	13 (36)
Diarrhea	10 (26)	1 (3)	12 (33)	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)

Lower Dose Quizartinib
Initial Results: QT Interval Prolongation*

	No. (%)		
	30 mg/day (N = 38)	60 mg/day (N = 36)	Total (N = 74)
Maximum value of QTcF (msec)			
> 450 to ≤ 480	16 (42)	17 (47)	33 (45)
> 480 to ≤ 500	2 (5)	5 (14)	7 (9)
> 500	2 (5)	1 (3)	3 (4)
Maximum change in QTcF from baseline (msec)			
> 30 to ≤ 60	18 (47)	13 (36)	31 (42)
> 60	1 (3)	7 (19)	8 (11)

*By central ECG review (readings >500 msec had to be confirmed to be classified as SAE)

Lower Dose Quizartinib

Initial Results: Comparison of 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 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%

Lower Dose Quizartinib Initial Results: Conclusions

- Sustained efficacy and decreased QT signal with lower doses of quizartinib
  - Efficacy
    - Substantial activity at both doses
  - Safety
    - Similar safety profile at 30 and 60 mg doses
    - QTcF prolongation dose dependent: decreased QTcF at 30 and 60 mg doses compared to prior Phase 2 Study at 90mg and 135 mg/day
- Next Step:
  - Global phase 3 randomized study of quizartinib in FLT3-ITD(+) patients in 1st relapse planned to start in early 2014

Lower Dose Quizartinib Acknowledgments

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Study Investigators:

UNITED STATES J. Altman, M. Baer, D. Claxton, J. Cortes, S. Goldberg, R. Larson, M. Levis, M. Litzow, A. Perl, G. Schiller, S. Strickland, R. Stuart, M. Tallman, C. Ustun

EUROPE C-E. Bulabois, M. Hunault-Berger, J-P. Marie, G. Martinelli, A. Pigneux, B. Quesnel, N. Russell, N. Vey