Effect of Co-Mutations and *FLT3*-ITD Variant Allele Frequency (VAF) on Response to Quizartinib or Salvage Chemotherapy (SC) in Relapsed/Refractory (R/R) Acute Myeloid Leukemia (AML)

Alexander E. Perl, MD[1], Jorge E. Cortes, MD[2], Siddhartha Ganguly, MD[3], Samer K. Khaled, MD[4], Alwin Krämer, MD[5], Giovanni Martinelli, MD[6], Nigel H. Russell, MD[7], Ken C.N. Chang, PhD[8], Kazunobu Kato, MD[8], Yuhu Yan, PhD[8], Li-An Xu, PhD[8], Sergey Korkhov[9], Tobias Guennel, PhD[9], Hiroyuki Sumi, PhD[10], Arnaud Lesegretain[8], Flora Berisha, MS[8], Derek Mires, PharmD[8], Aziz Benzohra, MD[11], Takeshi Isoyama, PhD[10], Cedric Dos Santos, PhD[8], Mark J. Levis, MD[12]

[1]Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; [2]Georgia Cancer Center, Augusta University, Augusta, GA; [3]The University of Kansas Health System, Kansas City, KS; [4]City of Hope National Medical Center, Duarte, CA; [5]Universität Heidelberg and German Cancer Research Center, Heidelberg, Germany; [6]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola (FC), Italy; [7]Nottingham University Hospital, Nottingham, United Kingdom; [8]Daiichi Sankyo, Inc., Basking Ridge, NJ; [9]Precision for Medicine Inc., Frederick, MD; [10]Daiichi Sankyo Co., Ltd., Tokyo, Japan; [11]Daiichi Sankyo France SAS, Paris, France; [12]The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD

BACKGROUND

- AML is a molecularly heterogeneous disease with a broad genomic landscape of driver mutations[1]
- *FLT3*-ITD mutations are associated with high relapse rates and reduced overall survival (OS) in patients with AML[2,3]
- Certain mutations commonly co-occur in patients with *FLT3*-ITD mutations, such as *NPM1* and *DNMT3A*[1]
  - These mutations alone or in combination can impact responses to chemotherapy, relapse rates, and survival[4,5]
  - The *NPM1* mutation conveys a favorable prognosis for newly-diagnosed patients receiving chemotherapy in the absence of *FLT3*-ITD or in those with low *FLT3*-ITD VAF[6]; less is known about the prognostic value of *NPM1* mutations in the R/R setting
  - Additionally, little is known about how these mutations affect response or survival with FLT3 inhibitors in R/R AML
- Quizartinib is an oral, highly potent, and selective FLT3 inhibitor (**Figure 1**)[7]
  - More potent in vivo than any other FLT3 inhibitor to date[8,9]
  - Nanomolar affinity (1.6 ± 0.7 nM) against FLT3[10]
  - Complete suppression of FLT3 phosphorylation in ex vivo plasma inhibitory assays[8]
  - Highly selective for FLT3 when screened against 402 human kinases (other kinases with K_d within 10-fold that of FLT3 were closely related receptor tyrosine kinases, eg, KIT)[10]
- Our goal was to determine whether co-mutations and/or *FLT3*-ITD VAF affected treatment responses and outcomes with quizartinib in the phase 3 QuANTUM-R study (**Figure 2**)[11]

Figure 1. Quizartinib is a Highly Potent and Selective *FLT3* Inhibitor

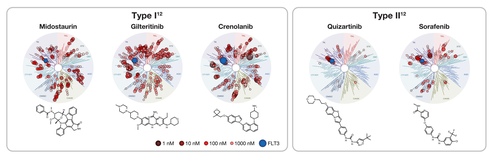
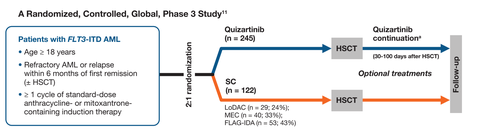
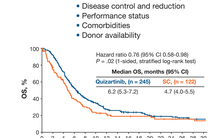


Figure 2. QuANTUM-R Study Design and Key Findings



Characteristic	Quizartinib (n = 245)	SC (n = 122)
Median age (range), years	55 (19-81)	58 (18-78)
Relapsed/refractory, %	67/33	66/34
Median duration of first CR (IQR), months	3.5 (2.4-4.7)	3.7 (2.4-4.6)
Median OS, months[a]	6.2	4.7
Best response		
CRc, n (%)[a]	118 (48)	33 (27)
CR, n (%)	10 (4)	1 (1)
CRp, n (%)	9 (4)	0
CRi, n (%)	99 (40)	32 (26)
Time to first CRc, median (range), months	1.1 (0.9-4.5)	0.9 (0.5-3.4)
Duration of CRc, median (95% CI), months	2.8 (2.4-6.2)	1.2 (0.8-2.9)
Transplant rate*, n (%)	78 (32)	14 (12)



- QuANTUM-R was the first study to demonstrate an OS benefit with a FLT3 inhibitor in patients with R/R *FLT3*-ITD–positive AML[11]
  - OS benefit was seen across patient subgroups and was reproduced consistently across sensitivity analyses
  - Transplant rates were higher with quizartinib (32%) compared with salvage chemotherapy (12%)

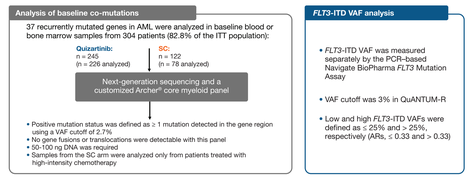
[a] Patients could resume quizartinib treatment 30 to 100 days after allogeneic HSCT per institutional policies and if certain conditions were met, including adequate blood count recovery and absence of significant graft-vs-host disease. [b] $P = .02$ (1-sided, stratified log-rank test). [c] Transplant rate is the percent of patients undergoing allogeneic HSCT directly following the protocol treatment with no intervening AML therapy.
CR, complete remission; CRc, composite complete remission; CRi, complete remission with incomplete hematologic recovery; CRp, complete remission with incomplete platelet recovery; EFS, event-free survival; FLAG-IDA, fludarabine, cytarabine, idarubicin, granulocyte-colony stimulating factor; HSCT, hematopoietic stem cell transplant; IQR, interquartile range; LoDAC, low-dose cytarabine; MEC, mitoxantrone, etoposide, cytarabine; OS, overall survival; R/R, relapsed/refractory; SC, salvage chemotherapy.

OBJECTIVE

- To investigate the effects of baseline co-mutations and *FLT3*-ITD VAF on OS and response (composite complete remission, CRc) to quizartinib and to SC in QuANTUM-R (**Figure 3**)

METHODS

Figure 3: Analyses Used in This Study



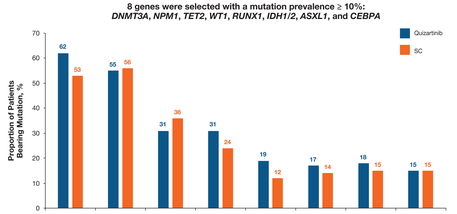
AR, allelic ratio; CRc, composite complete remission; ITT, intention-to-treat; OS, overall survival; SC, salvage chemotherapy; VAF, variant allele frequency.

RESULTS

Single gene analyses

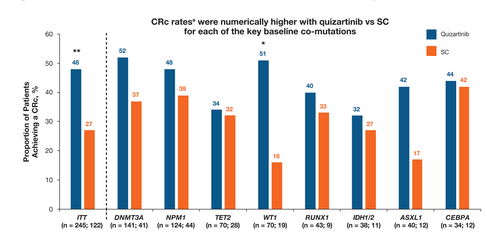
- 8 genes were selected with a baseline mutation prevalence ≥ 10% (**Figure 4**)
  - In addition to *FLT3*-ITD, the prevalence of key baseline co-mutations were 59.9% for *DNMT3A*^{mut} and 55.3% for *NPM1*^{mut}
- CRc rates were numerically higher with quizartinib vs SC for each of the key baseline co-mutations (**Figure 5**)
- Patients with *NPM1*^{mut} treated with quizartinib had a higher CRc rate than with SC (**Figure 5**), but similar OS (5.1 vs 4.7 months, respectively; HR, 0.954, $P = .82$; (**Figure 6**)
- In patients who had co-mutations in *DNMT3A*, *NPM1*, *WT1*, *RUNX1*, *IDH1/2* and *ASXL1*, OS was longer in quizartinib-treated patients than in those treated with SC (**Figure 6**)
- Of those with positive mutation status, patients with mutations in *CEBPA* had the longest OS duration, regardless of treatment with quizartinib or SC (**Figure 6**)
- Patients with *DNMT3A*^{mut} treated with quizartinib had a significantly longer OS vs SC (6.3 and 5.4 months, respectively; hazard ratio [HR], 0.652, $P < .05$; **Figure 7**)
- *NPM1*^{wt} patients had superior OS with quizartinib vs SC (**Figure 7**)

Figure 4. Prevalence of Co-Mutations at Baseline



All *P* values > .05; no statistical difference between treatment arms.
SC, salvage chemotherapy.

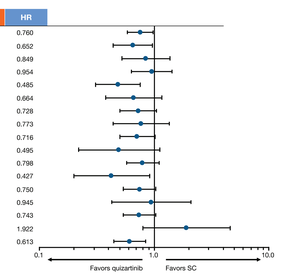
Figure 5. Prevalence of Co-Mutations at Baseline and Impacts on CRc Rate



[a] CRc rates comprised CR, CRp and CRi
* *P* < .01 vs SC, 2-sided *P* value for quizartinib vs SC based on non-stratified Cochran-Mantel-Haenszel test. ** *P* < .001 vs SC, 2-sided *P* value for quizartinib vs SC based on non-stratified Cochran-Mantel-Haenszel test.
CRc, composite complete remission; ITT, intention-to-treat; SC, salvage chemotherapy.

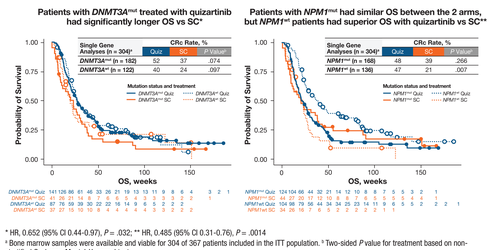
Figure 6. Impact of Baseline Co-Mutations on OS

Single Gene Analyses	Quizartinib	SC	HR
	Median OS, months		
ITT population (N = 367)	6.2	4.7	0.760
DNMT3A^{mut} (n = 182)	6.3	5.4	0.652
DNMT3A^{wt} (n = 122)	6.0	4.6	0.849
NPM1^{mut} (n = 168)	5.1	4.7	0.954
NPM1^{wt} (n = 136)	8.5	5.1	0.485
TET2^{mut} (n = 98)	6.2	3.0	0.664
TET2^{wt} (n = 206)	6.3	5.4	0.728
WT1^{mut} (n = 89)	6.0	4.0	0.773
WT1^{wt} (n = 215)	6.5	5.4	0.716
RUNX1^{mut} (n = 52)	6.3	5.2	0.495
RUNX1^{wt} (n = 252)	6.2	4.6	0.798
IDH1/2^{mut} (n = 49)	5.5	3.7	0.427
IDH1/2^{wt} (n = 255)	6.5	5.1	0.750
ASXL1^{mut} (n = 52)	5.8	4.5	0.945
ASXL1^{wt} (n = 252)	6.5	4.7	0.743
CEBPA^{mut} (n = 46)	8.5	8.7	1.922
CEBPA^{wt} (n = 258)	6.2	4.5	0.613



HR, hazard ratio; ITT, intention-to-treat; mut, mutant; OS, overall survival; SC, salvage chemotherapy; wt, wild-type.

Figure 7. Impact of Most Prevalent Baseline Co-Mutations on Treatment Outcome



* HR, 0.652 (95% CI 0.44-0.97), $P = .032$; ** HR, 0.485 (95% CI 0.31-0.76), $P = .0014$
[a] Bone marrow samples were available and viable for 304 of 367 patients included in the ITT population. [b] Two-sided *P* value for treatment based on non-stratified Cochrane-Mantel-Haenszel test.
CRc, composite complete remission; HR, hazard ratio; ITT, intention-to-treat; mut, mutant; OS, overall survival; SC, salvage chemotherapy; wt, wild-type.

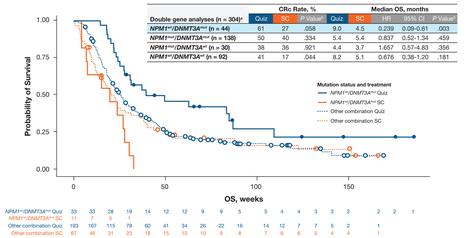
Double gene analyses

- Patients with *NPM1*^{wt}/*DNMT3A*^{mut} treated with quizartinib had the highest CRc rate and longest median OS (9.0 and 4.5 months, respectively; HR, 0.239, $P = .003$; **Figure 8**)

FLT3-ITD VAF analyses

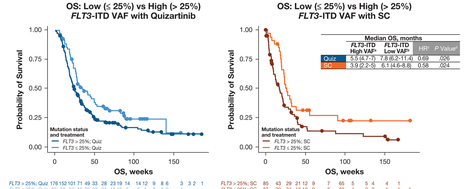
- Patients with high *FLT3*-ITD VAF have poor survival (**Figure 9**)
- OS benefit with quizartinib relative to SC was more pronounced among patients with high *FLT3*-ITD VAF (5.5 and 3.9 months, respectively; HR, 0.689, $P = .014$) than low *FLT3*-ITD VAF (7.8 and 6.1 months, respectively; HR, 0.857, $P = .535$; **Figure 10**)
- The OS benefit with quizartinib in patients with *NPM1*^{wt}/*DNMT3A*^{mut} was maintained in both low and high *FLT3*-ITD VAF groups (**Table 1**)
  - Similarly, for other *DNMT3A*/*NPM1* co-permutations, OS in both low and high *FLT3*-ITD VAF groups was consistent with OS in the co-mutation group

Figure 8. Impact of Baseline Permutations on OS



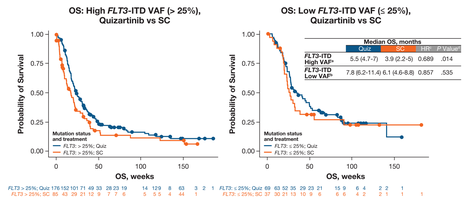
[a] Bone marrow samples were available and viable for 304 of 367 patients included in the ITT population. [b] Two-sided *P* value for treatment based on non-stratified Cochrane-Mantel-Haenszel test.
CRc, composite complete remission; HR, hazard ratio; ITT, intention-to-treat; mut, mutant; OS, overall survival; SC, salvage chemotherapy; wt, wild-type.

Figure 9. Impact of *FLT3*-ITD VAF on OS



[a] High *FLT3*-ITD VAF defined as VAF > 25%; [b] Low *FLT3*-ITD VAF defined as VAF < 25%; [c] HR *P* values based on Cox proportional hazard regression model; [d] 2-sided *P* value based on non-stratified Cochrane-Mantel-Haenszel test.
HR, hazard ratio; OS, overall survival; SC, salvage chemotherapy; VAF, variant allele frequency.

Figure 10. Impact of Treatment Arm and *FLT3*-ITD VAF on OS



[a] High *FLT3*-ITD VAF defined as VAF > 25%; [b] Low *FLT3*-ITD VAF defined as VAF < 25%; [c] HR *P* values based on Cox proportional hazard regression model; [d] 2-sided *P* value based on non-stratified Cochrane-Mantel-Haenszel test.
HR, hazard ratio; OS, overall survival; SC, salvage chemotherapy; VAF, variant allele frequency.

Table 1. Effect of Co-Mutations and *FLT3*-ITD VAF on Response to Quizartinib or SC

	CRc, %		Median OS, months			
	Quizartinib	SC	Quizartinib	SC	HR	95% CI
ITT Population (N = 367)[a]	48	27	6.2	4.7	0.76	0.58-0.98
Single Gene Analyses (n = 304)[b]						
DNMT3A^{mut} (n = 182)	52	37	6.3	5.4	0.652	0.44-0.97
DNMT3A^{wt} (n = 122)	40	24	6.0	4.6	0.849	0.53-1.37
NPM1^{mut} (n = 168)	48	39	5.1	4.7	0.954	0.63-1.44
NPM1^{wt} (n = 136)	47	21	8.5	5.1	0.485	0.31-0.76
TET2^{mut} (n = 98)	34	32	6.2	2.9	0.664	0.38-1.16
TET2^{wt} (n = 206)	54	30	6.3	5.4	0.728	0.51-1.05
CEBPA^{mut} (n = 46)	44	42	8.5	8.7	1.922	0.80-4.62
CEBPA^{wt} (n = 258)	48	29	6.2	4.5	0.613	0.45-0.84
IDH1/2^{mut} (n = 49)	32	27	5.5	3.7	0.427	0.20-0.92
IDH1/2^{wt} (n = 255)	51	31	6.5	5.1	0.75	0.54-1.04
Double Gene Analyses (n = 304)						
NPM1^{wt}/*DNMT3A*^{mut} (n = 44)	61	27	9.0	4.5	0.239	0.09-0.61
NPM1^{mut}/*DNMT3A*^{mut} (n = 138)	50	40	5.4	5.4	0.837	0.52-1.34
***FLT3*-ITD VAF Analyses**						
FLT3-ITD high VAF	50	19	5.5	3.9	0.689	0.51-0.93
FLT3-ITD low VAF	43	46	7.9	6.1	0.857	0.53-1.40
***FLT3*-ITD VAF Analyses in Selected Mutations**						
DNMT3A^{mut} high VAF	53	21	5.8	2.7	0.626	0.40-0.98
DNMT3A^{mut} low VAF	52	69	10.2	6.4	0.737	0.36-1.51
NPM1^{wt}/*DNMT3A*^{mut} high VAF	64	0	9.0	1.5	0.0179	0.002-0.16
NPM1^{wt}/*DNMT3A*^{mut} low VAF	55	50	11.3	6.2	0.372	0.11-1.23

[a] N = 367; quizartinib, n = 245; SC, n = 122; [b] Baseline bone marrow samples were available and viable from 304 of 367 patients in the ITT population

CONCLUSIONS

- While the presence of some mutations may influence frontline therapy choice, this is the first evaluation of the impact of baseline co-mutations on clinical outcomes in a large trial of patients with R/R *FLT3*-ITD–positive AML treated with quizartinib
- The survival benefit of quizartinib relative to salvage chemotherapy was most pronounced in patients with high *FLT3*-ITD VAF, compared with patients with low *FLT3*-ITD VAF
- Key co-mutations identified potentially affected treatment response and OS with quizartinib relative to those treated with salvage chemotherapy
  - Patients with *DNMT3A*^{mut} treated with quizartinib had significantly longer OS compared with those treated with salvage chemotherapy
  - Patients with *NPM1*^{mut} treated with quizartinib had a higher CRc rate, but not increased OS, than those treated with salvage chemotherapy
  - *CEBPA* mutations were uncommon, but associated with relatively long OS in this analysis, irrespective of treatment arm
- R/R patients with *NPM1*^{wt}/*DNMT3A*^{mut} co-mutations may particularly derive clinical benefit from quizartinib
- An independent dataset is necessary to validate whether discrete genotypes show survival benefits with quizartinib over SC

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DISCLOSURES

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