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POSTER ABSTRACTS

615.ACUTE MYELOID LEUKEMIAS: COMMERCIALLY AVAILABLE THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Quantum-First (Q-F): Clinical Bridging Study for FMS-like Tyrosine Kinase 3-Internal Tandem Duplication (*FLT3*-ITD) Companion Diagnostic Development

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Background

Q-F (NCT02668653) showed that the highly potent, selective, type 2 FLT3 inhibitor quizartinib (Q) + standard chemotherapy ± transplantation, followed by Q monotherapy for ≥36 cycles, reduced the relative risk of death by 22.4% vs placebo (P) in newly diagnosed (nd) *FLT3*-ITD+ AML, with HR of 0.776 and *P* value of 0.0324 (PMID: 37116523). In Q-F, *FLT3*-ITD mutation status was determined using a *FLT3*-ITD mutation detection clinical trial assay (CTA) validated under design control by Navigate BioPharma Services, Inc. We describe the results of the bridging study, aimed to show agreement between the CTA & the LeukoStrat CDx *FLT3* Mutation Assay (CDx, by Invivoscribe) in *FLT3*-ITD+ pt selection and to determine if Q efficacy (overall survival [OS]) was maintained in nd *FLT3*-ITD+ AML pts from Q-F, if pts had been selected using the CDx.

Methods

In both CTA & CDx, DNA, extracted from bone marrow (n=884 each) or peripheral blood (n=139 each), was amplified via PCR and amplicons were detected via capillary electrophoresis. A sample was considered CTA+ if the variant allele frequency (*FLT3*-ITD/total *FLT3*) was ≥3% and CDx+ if the signal ratio (SR; *FLT3*-ITD/ *FLT3* WT) was ≥0.05. The agreement between CTA & CDx was based on evaluating CTA+ & CTA− samples with the CDx assay. A primary analysis included the CDx detected (CDx+ & CDx−) and the CDx invalid results. A secondary analysis used CDx+ and CDx− results only. To establish agreement between CDx & CTA, positive % agreement (PPA) and negative % agreement (NPA) were determined using CTA results as reference for the agreement analysis set (AAS). Concordance was established if the lower bounds of the 95% CIs for both PPA & NPA exceeded 90% for the analysis that included the invalid CDx results. Median OS in the subgroups was calculated based on Kaplan-Meier estimates. Stratified Cox proportional hazards regression model was used to estimate HRs, 95% CI, and *P* value.

Results

Full analysis set (N=3468) included all Q-F screened CTA+ pts (n=863), all screened CTA− pts (n=2556), and pts with unknown CTA status not eligible for randomization due to other criteria (n=49). Of these, 1032 pts formed the primary analysis set (PAS), including all pts randomized in Q-F with samples available for CDx testing (N=513: Q, n=254; P, n=259) and a randomly selected subset of CTA− pts (n=519). The ascertainment rate was 95.2% (513/539), as 26 of the 539 pts randomized in Q-F were excluded from the bridging study. Within the PAS, 3 samples were not tested by CDx due to insufficient volume/DNA amount. The AAS (N=1029: CTA+, n=513; CTA−, n=516) included pts in the PAS with valid CTA results and tested with CDx. In the AAS, 6 samples (3 CTA+, 3 CTA−) did not yield valid CDx results, resulting in 1023 CDx-evaluable total pts (CTA+, n=510; CTA−, n=513). Among 510 CTA+ samples, 483 were CDx+. Among 513 CTA− samples, 513 were CDx−. Therefore,

996 samples yielded concordant results, 27 samples yielded discordant results, and 6 samples did not yield a valid CDx result for comparison. Point estimates of PPA & NPA were 94.2% & 99.4%, respectively, with invalid CDx results included in the calculation, and 94.7% & 100%, respectively, without invalid CDx results. The lower bounds of the 95% CIs were all above the corresponding acceptance criterion of 90% for PPA & NPA (Table 1). In Q-F, the prevalence of CTA+ was 24.9% among screened pts (863/3468), whereas in the bridging study, 49.9% (510/1023) of pts were CTA+: this enrichment in CTA+ pts could lead to a biased estimate of the agreement between CDx & CTA when using CDx as reference. The positive predictive value (PPV) and negative predictive value (NPV) of the CDx adjusted for this enrichment ± invalid CDx results, showed that the lower bounds of the 95% CIs were all >95% (Table 1). The efficacy OS analysis in the intent-to-treat (ITT) CDx+ population (ITT CDx+=CTA+ & CDx+; N=483: Q, n=242; P, n=241) demonstrated a clinically relevant OS improvement with Q (median OS of 29.4 months) vs P (median OS of 14.8 months), resulting in 14.6 months prolongation of median OS, with an HR of 0.794 (95% CI 0.621-1.014), corresponding to a 20.6% reduction in relative risk of death (Figure 1).

Conclusions

This study showed 1) agreement between CDx & CTA in identifying nd *FLT3*-ITD+ AML pts and 2) that OS benefit provided by Q in the ITT CDx+ population is comparable with the OS benefit in the ITT population of Q-F. The LeukoStrat CDx *FLT3* Mutation Assay aids in assessing AML pts for Q therapy.

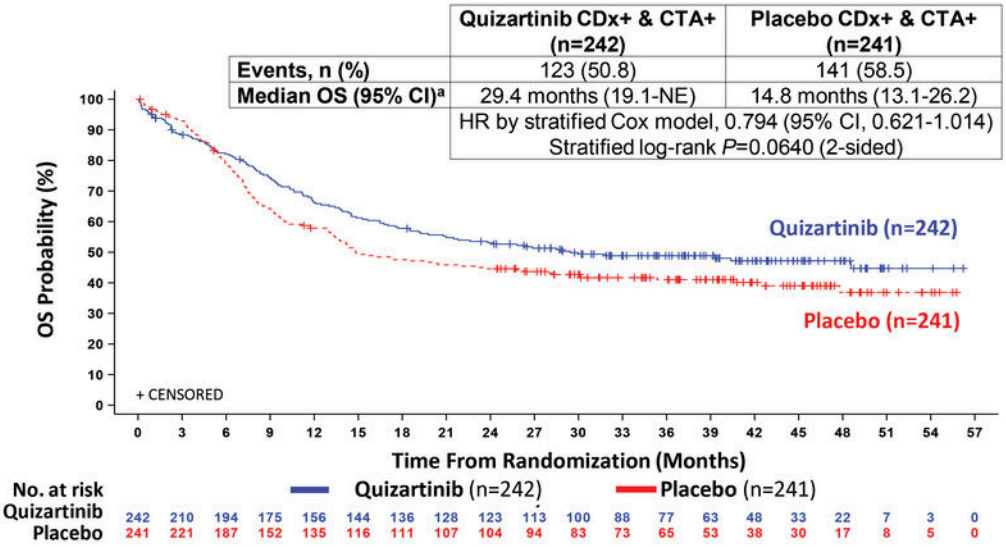
Disclosures Rohrbach: *Daiichi Sankyo:* Current Employment, Current holder of *stock options* in a privately-held company. **Chang:** *Daiichi Sankyo:* Current Employment, Current holder of *stock options* in a privately-held company. **Karnoub:** *Daiichi Sankyo:* Current Employment, Current holder of *stock options* in a privately-held company. **Liu:** *Daiichi Sankyo Inc.:* Current Employment. **Kamel:** *Daiichi Sankyo Inc.:* Consultancy, Other. **Khambata-Ford:** *Daiichi Sankyo Inc.:* Current Employment. **Rivera:** *Navigate BioPharma Services Inc.:* Current Employment. **Lameh:** *Navigate BioPharma Services, Inc.:* Current Employment. **Rudenko:** *Invivoscribe, Inc.:* Current Employment. **Todt:** *Invivoscribe, Inc.:* Current Employment. **Gerhold:** *Invivoscribe, Inc:* Current Employment. **Huang:** *Invivoscribe, Inc:* Current Employment, Current holder of *stock options* in a privately-held company. **Miller:** *Invivoscribe, Inc:* Current Employment, Current equity holder in private company, Current holder of *stock options* in a privately-held company. **Perl:** *Forma:* Consultancy; *Syndax:* Research Funding; *Bayer:* Research Funding; *Foghorn:* Consultancy; *BMS:* Honoraria; *Immunogen:* Honoraria; *FujiFilm:* Research Funding; *Abbvie:* Consultancy, Honoraria, Research Funding; *Astellas:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *BerGen Bio:* Honoraria; *Beat AML:* Other: Participation on a Data Safety Monitoring Board or Advisory Board; *Genentech:* Honoraria; *Aptose:* Honoraria; *Daiichi-Sankyo:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Rigel:* Honoraria; *Actinium:* Honoraria. **Levis:** *FujiFilm:* Research Funding; *Takeda:* Consultancy; *Menarini:* Consultancy; *Jazz:* Consultancy; *Daiichi-Sankyo:* Consultancy; *Bristol Myers Squibb:* Consultancy; *Amgen:* Consultancy; *Abbvie:* Consultancy; *Astellas Global Pharma:* Research Funding; *Pfizer:* Consultancy. **Ito:** *Daiichi Sankyo Inc.:* Current Employment.

Table 1. Agreement Between CDx and CTA

Measure of Agreement Based on CTA Results (AAS)	Without Invalid CDx Results		With Invalid CDx Results[a]	
	Percent Agreement (n/N)	95% CI[b]	Percent Agreement (n/N)	95% CI[b]
PPA	94.7 (483/510)	92.4-96.5	94.2 (483/513)	91.8-96.0
NPA	100.0 (513/513)	99.3-100.0	99.4 (513/516)	98.3-99.9
Measure of Agreement Adjusted for Enrichment[c]	**Without Invalid CDx Results**		**With Invalid CDx Results[a]**	
	Percent Agreement	95% CI[d]	Percent Agreement	95% CI[d]
PPV	100.0	100.0-100.0	98.2	95.9-100.0
NPV	98.3	97.6-98.9	98.1	97.4-98.7

[a]Invalid CDx results used as discordant results.
[b]Calculated using the exact (Clopper-Pearson) method.
[c]Prevalence of CTA+ set as 25%.
[d]Calculated using non-parametric bootstrapping method.
AAS, agreement analysis set; CDx, LeukoStrat CDx *FLT3* Mutation Assay; CTA, Navigate, Daiichi Sankyo Clinical Trial Assay; PPA, positive percent agreement; PPV, positive predictive value; NPA, negative percent agreement; NPV, negative predictive value.

Figure 1: Kaplan-Meier Plot of OS in the ITT CDx+ Analysis Set (CTA+ & CDx+)



[a]Calculated using the Brookmeyer and Crowley method.
CDx, LeukoStrat CDx *FLT3* Mutation Assay; CTA, Navigate, Daiichi Sankyo Clinical Trial Assay; HR, hazard ratio; ITT, intent-to-treat; NE, not estimable; OS, overall survival.

Figure 1

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