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ORAL ABSTRACTS

617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Post-Hoc Analysis of Measurable Residual Disease from BMT-CTN 1506/Morpho: FLT3-ITD Variant Allele Frequency and Survival Are Highly Correlated

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Background:
BMT CTN 1506/MORPHO was a randomized study of the FLT3 inhibitor gilteritinib versus placebo as post-transplant (HCT) maintenance therapy for patients (pts) with *FLT3-ITD* acute myeloid leukemia (AML). Patients with *FLT3-ITD* AML in first remission underwent HCT and then were randomized, in double-blind fashion, to either gilteritinib or placebo for 24 months. The primary endpoint was relapse-free survival (RFS), and a pre-specified secondary endpoint was the effect of measurable residual disease (MRD) on survival as detected by a highly sensitive assay for *FLT3-ITD* mutations. In the primary analysis, while RFS was higher for pts randomized to gilteritinib, the difference did not reach the pre-determined threshold for significance (HR: 0.679; 95% CI: 0.459, 1.005; 2-sided p-value: 0.0518). However, in the secondary analysis, the 50.6% of pts who had MRD detectable pre- or post-HCT had significantly higher RFS with gilteritinib (HR of relapse or death=0.515, 95% CI: 0.316, 0.838, p = 0.0065). In this post-hoc analysis, we examined 1) the impact on RFS of different levels of *FLT3-ITD* variant allele frequency (VAF) pre-randomization (immediately before or after HCT but prior to randomization to gilteritinib or placebo); 2) the impact of the presence of multiple mutations detected as MRD pre-HCT; and 3) the eradication of *FLT3-ITD* clones detected post-HCT during follow up on gilteritinib or placebo.
Methods:
First-pull marrow aspirates were collected from pts at two time points pre-randomization (pre-HCT and between 30-90 days post-HCT), as well as at 3, 6, 12, 18, and 24 months post-randomization. For MRD detection (performed at Invivoscribe; San Diego, CA), 700 ng input DNA was amplified by polymerase chain-reaction (PCR) using 25 cycles and primers flanking exons 14 and 15 of *FLT3*, followed by next-generation sequencing (NGS) analysis of the amplicons. Variant allele frequency (VAF) was calculated as *FLT3* mutant reads/total *FLT3* reads. For pts with multiple *FLT3-ITD* mutations, the VAF used in analysis was the sum of the VAFs for each *FLT3-ITD* variant. The lower limit of blank (LOB) of the assay is estimated to be 1×10^{-6} VAF. For terminology, VAF $> 1 \times 10^{-6}$ and $< 1 \times 10^{-5}$ is referred to as MRD6, VAF $> 1 \times 10^{-5}$ and $< 1 \times 10^{-4}$ is MRD5, VAF $> 1 \times 10^{-4}$ or greater is MRD4, and MRD0 equals no detectable MRD.
Results:
MRD was evaluated in 350/356 (98.3%) pts pre-HCT and 347/356 (97.5%) pts post-HCT. MRD was detected in 46% of pts pre-HCT and 19.9% prior to randomization, including 4.5% who did not have detectable MRD pre-HCT. The variant allele frequency (VAF) of detectable MRD ranged from a low of 1.09×10^{-6} to a high of 3.0×10^{-1}. More than a single mutation was detected in 51 pts pre-HCT. Most of these 51 pts had 2 clones, but the total ranged from 2-9. The presence of more than one mutation detected as MRD immediately pre-HCT was associated with worse RFS compared with all other pts (MRD-positive with only one clone and MRD-negative), irrespective of treatment arm (Figure 1A; HR=2.428, 95% CI: 1.555, 3.792, $P < 0.001$). There was no significant difference in age, mutation length, VAF, or karyotype between pts with more than one mutation and those with single mutations. However, if the VAFs of pts with multiple *FLT3-ITD* mutations were summed and treated as a single value, then the median VAF for pts with multiple mutations was higher than for those with single mutations (2.14×10^{-4} vs. 3.12×10^{-5}). The VAF (including the summed VAFs of pts with multiple mutations) at multiple levels correlated very closely with RFS after HCT. To illustrate this quantitative effect of peri-HCT *FLT3-ITD* VAF on RFS, Kaplan-Meier analysis of pts on the placebo arm grouped by MRD level is displayed in Figure 1B. In the 71 pts with MRD detectable post-HCT, the MRD was eradicated in 69% of pts on gilteritinib versus 44% of pts on placebo.
Conclusions
Pts with multiple *FLT3-ITD* mutations have a worse prognosis, which may simply be a reflection of increased disease burden (VAF). The quantity of *FLT3-ITD* MRD appears to highly correlate with outcome. Gilteritinib appears to augment the effect of HCT, as evidenced by increased eradication of MRD post-HCT. These data illustrate the potential utility of the PCR-NGS *FLT3-ITD* MRD assay in the management of pts with *FLT3-ITD* AML.

Disclosures Levis: *Daiichi-Sankyo:* Consultancy; *Bristol Myers Squibb:* Consultancy; *Abbvie:* Consultancy; *Jazz:* Consultancy; *Astellas Global Pharma:* Research Funding; *FujiFilm:* Research Funding; *Amgen:* Consultancy; *Menarini:* Consultancy; *Takeda:* Consultancy; *Pfizer:* Consultancy. **Hamadani:** *Novartis:* Consultancy; *SeaGen:* Consultancy; *MorphoSys:* Consultancy; *Legend Biotech:* Consultancy; *Sanofi Genzyme:* Speakers Bureau; *Myeloid Therapeutics:* Honoraria; *Genentech:* Honoraria; *Takeda:* Research Funding; *Spectrum Pharmaceuticals:* Research Funding; *Astellas:* Research Funding; *BeiGene:* Speakers Bureau; *Astra Zeneca:* Speakers Bureau; *Kadmon:* Consultancy; *Genmab:* Consultancy; *Incyte:* Consultancy; *Gamida Cell:* Consultancy; *BeiGene:* Speakers Bureau; *Kite, a Gilead Company:* Consultancy, Speakers Bureau; *AstraZeneca:* Speakers Bureau; *Caribou:* Consultancy; *Bristol Myers Squibb:* Consultancy; *Genmab:* Consultancy; *CRISPR:* Consultancy; *Omeros:* Consultancy; *Abbvie:* Consultancy; *ADC therapeutics:* Consultancy, Honoraria, Research Funding, Speakers Bureau. **Logan:** *Enlivex:* Consultancy. **Wingard:** *Takeda:* Consultancy; *F2G:* Consultancy; *Celgene:* Consultancy; *Cidara:* Consultancy; *Orca:* Consultancy. **Perl:** *Daiichi-Sankyo:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Genentech:* Honoraria; *Syndax:* Research Funding; *Immunogen:* Honoraria; *Foghorn:* Consultancy; *BMS:* Honoraria; *BerGen Bio:* Honoraria; *Forma:* Consultancy; *Aptose:* 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; *Bayer:* Research Funding; *Beat AML:* Other: Participation on a Data Safety Monitoring Board or Advisory Board; *Rigel:* Honoraria; *Actinium:* Honoraria. **Soiffer:** *NMPD - Be the Match, USA:* Membership on an entity's Board of

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OffLabel Disclosure: Gilteritinib is currently approved only for relapsed/refractory FLT3-mutated AML. This trial explores its use as post-transplant maintenance.

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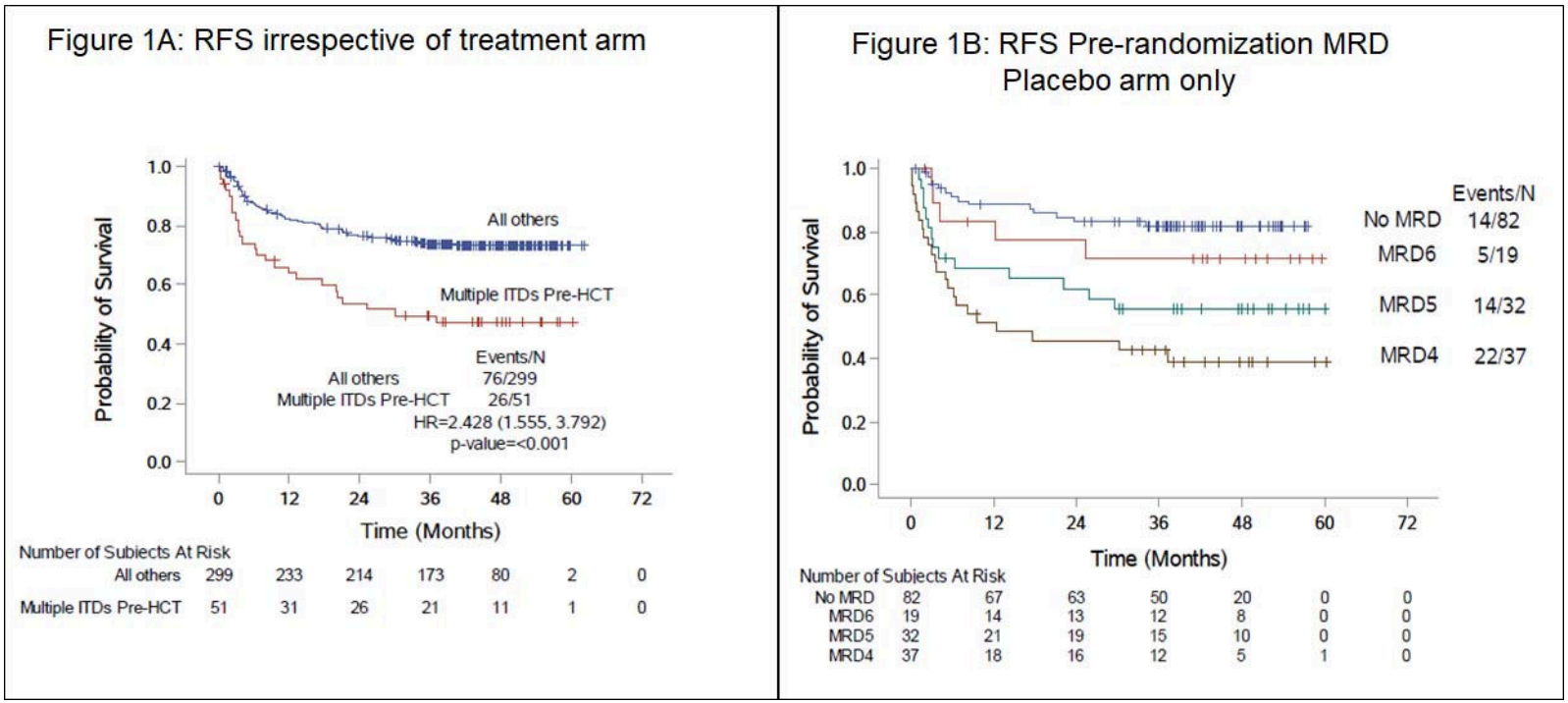

Figure 1