Publication Number: 343

Abstract Title : Validation of measurable residual disease as a surrogate endpoint in acute myeloid leukemia: A HARMONY Alliance study of European randomized trials

Category: 600s - Hematologic Malignancy

Review Category: 619. Acute Myeloid Leukemias: Disease Burden and Measurable Residual Disease in Prognosis and Treatment

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Abstract Body

Introduction: Measurable residual disease (MRD) prior to consolidation therapy is a strong prognostic biomarker for relapse and long-term survival in acute myeloid leukemia (AML). Beyond its prognostic role, MRD is increasingly used to guide therapeutic decisions. A logical next step is regulatory acceptance of MRD as a (co-)primary endpoint in AML, as recently granted by the FDA for MRD in multiple myeloma. However, acceptance in AML is hampered by disease heterogeneity, variability in MRD assessments and a lack of trial-level validation. As MRD-guided treatment becomes more common, future trial outcomes may be confounded by such interventions. Thus, establishing MRD now as a surrogate endpoint is critical to enable accelerated drug approval in AML. Here, we evaluate both individual- and trial-level surrogacy of MRD assessed by multiparameter flow cytometry (MFC) and qPCR for mutant *NPM1* using harmonized patient-level data from seven prospective randomized phase II/III trials.

Methods: We included patient-level data from 1,858 adult with AML enrolled in trials conducted by AMLSG, HOVON-SAKK, SAL, and UK-NCRI, collected through the HARMONY Alliance. Eligible trials involved randomization to experimental or placebo treatment added to a standard intensive induction chemotherapy, with ≥20 patients per arm and per MRD subgroup. Patients were included if they had a MRD assessment after two chemotherapy cycles by either MFC or qPCR for mutant *NPM1*. Data were harmonized using the OMOP common data model. Following FDA guidance, we analyzed two levels of surrogacy. For individual-level surrogacy, we examined the association between MRD status and overall

survival (OS) using Plackett's copula models and multivariable Cox regression. For trial-level surrogacy, we quantified the relationship between treatment effects on MRD and OS using hazard ratios (HR) and odds ratios (OR) in weighted least-squares regression. A coefficient of determination (R^2) >0.8 with 95% CI lower bound >0.6 was considered strong trial-level surrogacy, consistent with previously accepted surrogate endpoints. Subgroup analyses were conducted by MRD method and transplant status.

Results: The included trials were AMLSG 09-09 (qPCR MRD assessment), three HOVON-SAKK trials (AML-102, AML-103, AML-132; all MFC), the SAL cohort (qPCR), and the UK-NCRI AML17 trial, which included two separate randomizations (both MFC- and qPCR-MRD).
In multivariable analysis, MRD positivity was associated with significantly worse OS across the cohort (HR: 1.66, 95% CI: 1.33–2.07, p<0.001). This association persisted when stratified by MRD method or treatment arm (placebo vs experimental). The global OR for the association between MRD status and OS was 0.39 (95% CI: 0.32–0.47); among transplanted patients, OR was 0.61 (95% CI: 0.42–0.81), and among non-transplanted patients, 0.33 (95% CI: 0.25–0.41).
Trial-level surrogacy analysis was limited to MFC-based MRD (n= 1,268) due to the limited number of qPCR-based trials. The overall R^2 between treatment effect on MRD (OR) and OS (HR) was 0.91 (95% CI: 0.56–1.00), suggesting strong surrogacy, though the lower confidence interval bound fell below the predefined threshold. When restricting to non-transplanted patients, R^2 increased to 0.99 (95% CI: 0.94–1.00), whereas among transplanted patients R^2 was 0.54 (95% CI: 0.00–1.00), suggesting that transplant may attenuate the association between MRD and OS at the trial level.

Conclusions: This pooled analysis represents the largest MRD dataset in AML to date and demonstrates that MRD after induction is a robust individual-level predictor of OS, whether measured by MFC or qPCR for *NPM1*. MRD retained prognostic value across treatment arms and in multivariable models. These findings reflect strong individual-level surrogacy: MRD-negative patients were more than twice as likely to survive as MRD-positive patients, although this difference was less pronounced in transplanted patients, suggesting that allogeneic transplant may partially mitigate the adverse impact of MRD positivity. Importantly, trial-level surrogacy was confirmed for MFC-MRD in non-transplanted patients, supporting its use as an intermediate endpoint reasonably likely to predict long-term outcomes in intensively treated AML patients. As MRD-guided therapy and maintenance strategies become standard, this harmonized prospective dataset provides timely evidence to support MRD as a regulatory surrogate endpoint for AML drug development.

Keywords: Acute Myeloid Malignancies, Myeloid Malignancies, Measurable Residual Disease , Diseases, Human, Adult, AML, Study Population, Translational Research, Research

Disclosure : Jesse Tettero: None declared, Sträng Eric: None declared, Sylvie Freeman: Celgene, Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: Yes, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: No, MPAACT, Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: No, Bristol Myers Squibb, Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: Yes, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: No, AstraZeneca, Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: Yes, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: No, Cytek, Consultancy (Includes expert testimony): No, Patents & Royalties: No,

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months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Pfizer, Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock

options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Rarity, Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Javier Martinez Elicegui: None declared, Rabea Mecklenbrauck: None declared, Klaus Metzeler: Menarini Stemline, Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Servier, Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, AstraZeneca, Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, BMS, Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Otsuka, Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: No, AbbVie, Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: Yes, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Novartis, Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Daiichi Sankyo, Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Sysmex, Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Janssen, Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Jazz Pharmaceuticals, Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Astellas, Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder

in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Pfizer, Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Marta Sobas: Novartis, Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Bristol Myers Squibb (BMS), Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Aop Orphan Pharmaceuticals Poland, Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, GlaxoSmithKline (GSK), Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Sobi, Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Ian Thomas: None declared, Amin Turki: Neovii Biotech, Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: Yes, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: No, Ground Truth Labs, Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: Yes, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: No, Pfizer, Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: No, Biomarin, Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: No, CSL Behring, Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: No, Maat Pharma, Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: No, onkowissen.tv, Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research

Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: No, Laura Tur Gimenez: None declared, Brain Huntley: None declared, Nigel Russell: None declared, Jurjen Versluis: None declared, Hartmut Döhner: Pfizer, Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Syndax Pharmaceuticals, Inc., Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Bristol Myers Squibb, Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: Yes, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: No, Jazz Pharmaceuticals, Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: Yes, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, AbbVie (incl. travel/accommodation), Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: Yes, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Otsuka, Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: No, Servier (incl. travel/accommodation), Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: Yes, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Astellas, Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: Yes, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: No, Jesus Maria Hernandez Rivas: Pfizer, Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: Yes, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: No, GSK, Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: Yes, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Amgen, Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Lars Bullinger: Celgene/BMS, Novartis, Abbvie, Gilead, Astellas, Jazz Pharmaceuticals, Bayer, Pfizer, Janssen, Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No,

Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: Yes, Gert J. Ossenkoppele: AbbVie, Agios, Amgen, Astellas, Celgene, Daiichi Sankyo, Jazz, Novartis, Pfizer, and Roche, Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: No, BD, Celgene, Genentech, Johnson & Johnson, and Novartis., Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: Yes, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: No