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POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Molecular Measurable Residual Disease (MRD) Clearance (≤1%) Is Associated with Improved Clinical Outcomes in Patients with Higher-Risk Myelodysplastic Neoplasms (HR-MDS): An Exploratory Analysis of Stimulus-MDS1 in Patients Receiving Sabatolimab or Placebo + Hypomethylating Agent (HMA)

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Background: Sabatolimab (MBG453) is a novel immunotherapy targeting TIM-3, an immuno-myeloid regulator expressed on both immune and leukemic stem cells. In the randomized, double-blind, placebo-controlled, Phase (Ph) II STIMULUS-MDS1 study (NCT03946670) in patients (pts) with HR-MDS, although improvements in complete remission (CR) and progression-free survival (PFS) were not statistically significant, sabatolimab + HMA was associated with longer duration of response (DoR), and the data suggest a delayed-onset benefit in the sabatolimab arm, as well as a potential treatment effect in pts with lower disease burden (Zeidan AM, et al. ASH 2022). The clinical significance of MRD in HR-MDS is not well established. We report an exploratory analysis of mutational clearance and MRD by next-generation sequencing (NGS) to evaluate the association with clinical outcomes.

Methods: Treatment-naive pts aged ≥18 years with intermediate (+ ≥5% bone marrow [BM] blasts), high or very high risk MDS by Revised International Prognostic Scoring System were randomized to sabatolimab or placebo added to azacitidine/decitabine (Zeidan AM, et al. ASH 2022). Peripheral blood (PBMC) and/or BM mononuclear cell (BMMC) samples were collected and NGS performed on genomic DNA extracted from baseline (BL) and on-treatment samples using a 38-gene NGS-error-corrected panel with sensitivity of 2% and 0.2% variant allelic frequency (VAF), respectively. Concordance and correlation between PBMC and BMMC were assessed. The prognostic value of clonal clearance at different VAF cut-offs (0.2%, 0.5% or 1%) was assessed. MRD-x status was defined as any mutation call above VAF cut-off x, excluding mutations in *DNMT3A, TET2* and *ASXL1* (*DTA*). Association between MRD status and clinical outcomes was analyzed regardless of treatment to increase sample and used best overall response, 6-month landmark analysis, and a time-dependent Cox model to rule out immortal bias.

Results: NGS was run on 332 BMMC samples from 112 pts and 439 PBMC samples from 123 pts (127 pts randomized). 112 pts had ≥1 qualifying BL mutation (NGS cohort) and 106 pts (sabatolimab + HMA, N=56; placebo + HMA, N=50) had ≥1 at follow-up (MRD cohort). BL characteristics were balanced between NGS/MRD cohorts and between treatments in the MRD cohort.

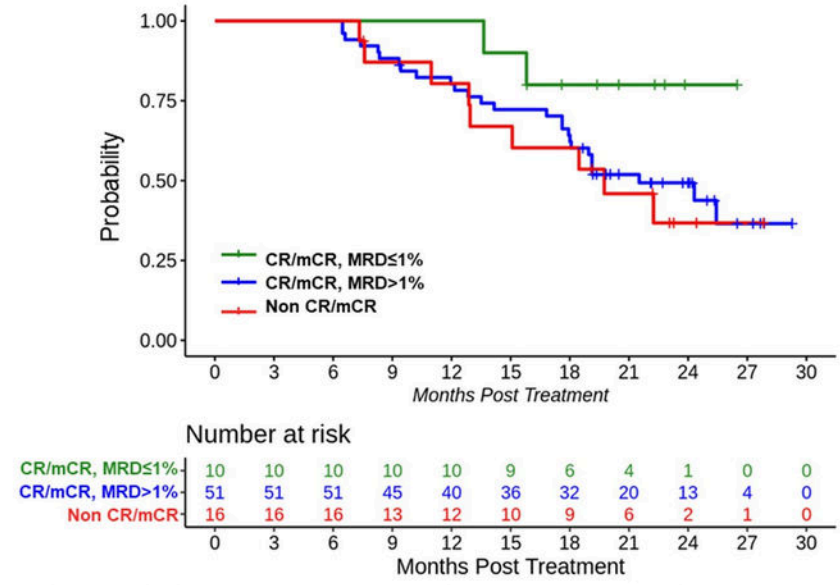
Overall agreement in mutation calling at variant level between BMMC and PBMC was >97% (8312/8566 total mutation calls), with >88% positive (817/926) and >98% negative agreement (7495/7640). Across reported mutated variants (N=817), there was good correlation (pearson cor=0.88) in VAF between BMMC and PBMC. When considering all paired samples, concordance of best MRD status using PBMC or BMMC results at the pt level (N=95) was: MRD-0.2, 97%; MRD-0.5, 89%; MRD-1, 90%. Given good PBMC and BMMC agreement, results were combined (higher VAF used if both) for outcomes analysis.

In the MRD cohort, 11% (N=12), 18% (N=19) and 27% (N=29) of pts achieved MRD-0.2, MRD-0.5 and MRD-1 negativity, respectively. Most pts with MRD-0.2, -0.5 and -1 clearance had documented response of CR/marrow CR [mCR] (>80%) or CR/partial remission [PR]/hematologic improvement [HI] (>75%). Best overall response of MRD-1 negativity achieved anytime on treatment was associated with improved PFS and overall survival (OS) in the overall population and for responding pts (CR/mCR or CR/PR/HI). Similar results were obtained in a landmark analysis at 6 months (**Fig 1**). This was supported by a

time-dependent Cox-model indicating that MRD-x negativity was associated with a lower hazard ratio for PFS and OS vs MRD-x positivity (**Fig 2**).
A consistently higher proportion of pts in the sabatolimab (N=56) vs placebo (N=50) arms had on-treatment mutation clearance at different cut-offs: MRD-0.2, 16.1% vs 6.0%; MRD-0.5, 25.0% vs 10.0%; MRD-1, 35.7% vs 18.0%, respectively.
Conclusions: We present the first results from a prospective, controlled, randomized study demonstrating the potential prognostic value of MRD for PFS and OS in HR-MDS. Our results demonstrate high NGS concordance between PBMC and BMMC on-treatment samples, indicating that PBMC could represent an alternative for clonal monitoring. Interestingly, more pts treated with sabatolimab + HMA reached MRD negativity while in remission, potentially explaining the longer DoR in pts receiving sabatolimab + HMA vs placebo + HMA. These findings will be further explored in the ongoing Ph III STIMULUS-MDS2 study (NCT04266301).

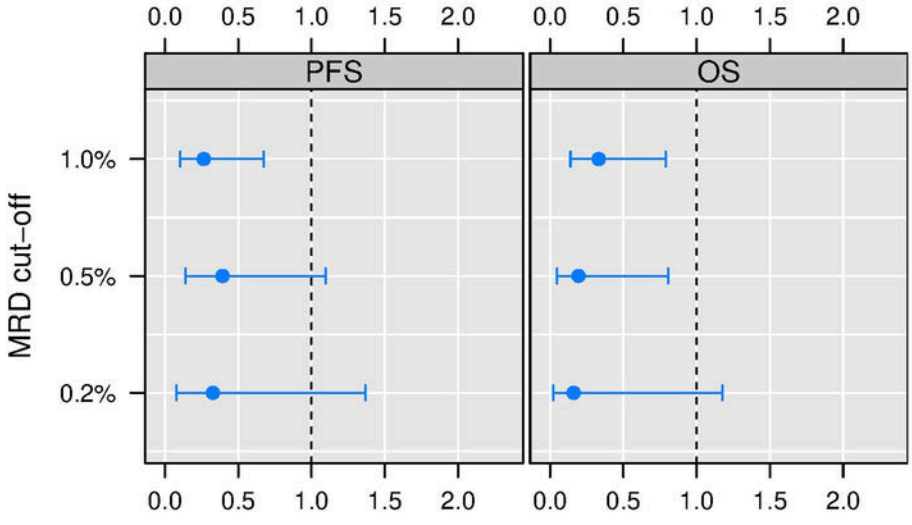
Disclosures Zeidan: *Schrödinger:* Consultancy, Honoraria; *Notable:* Consultancy, Honoraria; *Chiesi:* Consultancy, Honoraria; *Mendus:* Consultancy, Honoraria; *Otsuka:* Consultancy, Honoraria; *Foran:* Consultancy, Research Funding; *Syros:* Consultancy, Honoraria; *ALX Oncology:* Consultancy, Honoraria; *Kura:* Consultancy, Honoraria; *Seattle Genetics:* Consultancy, Honoraria; *Servier:* Consultancy, Honoraria; *Boehringer-Ingelheim:* Consultancy, Honoraria; *Jazz:* Consultancy, Honoraria; *Orum:* Consultancy, Honoraria; *Geron:* Consultancy, Honoraria; *Syndax:* Consultancy, Honoraria; *Gilead:* Consultancy, Honoraria; *Zentalis:* Consultancy, Honoraria; *BeyondSpring:* Consultancy, Honoraria; *Incyte:* Consultancy, Honoraria; *Pfizer:* Consultancy, Honoraria; *Celgene/BMS:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria; *Amgen:* Consultancy, Honoraria; *Shattuck Labs:* Research Funding; *Agios:* Consultancy, Honoraria; *Daiichi Sankyo:* Consultancy, Honoraria; *Tyme:* Consultancy, Honoraria; *Taiho:* Consultancy, Honoraria; *AbbVie:* Consultancy, Honoraria; *Ionis:* Consultancy, Honoraria; *Takeda:* Consultancy, Honoraria; *Genentech:* Consultancy, Honoraria; *Epizyme:* Consultancy, Honoraria; *Astex:* Research Funding; *Lox Oncology:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria; *Astellas:* Consultancy, Honoraria; *BioCryst:* Consultancy, Honoraria; *Regeneron:* Consultancy, Honoraria. **Fenaux:** *Novartis:* Consultancy, Honoraria, Research Funding; *Bristol Myers Squibb:* Consultancy, Honoraria, Research Funding; *Jazz:* Consultancy, Honoraria, Research Funding; *French MDS Group:* Honoraria; *Janssen:* Consultancy, Honoraria, Research Funding; *AbbVie:* Consultancy, Honoraria, Research Funding. **Han:** *Novartis:* Current Employment. **James:** *Novartis:* Current Employment. **Malek:** *Novartis:* Current Employment. **Marques Ramos:** *Novartis:* Current Employment. **Miyazaki:** *Novartis:* Honoraria; *Celgene:* Honoraria; *Dainippon-Sumitomo:* Honoraria; *Nipponshinnyaku:* Honoraria; *Chugai:* Honoraria; *Otsuka:* Honoraria; *Astellas:* Honoraria; *Kyowa-Kirin:* Honoraria. **Platzbecker:** *Geron:* Consultancy, Research Funding; *Janssen Biotech:* Consultancy, Research Funding; *Novartis:* Consultancy, Honoraria, Research Funding; *Curis:* Consultancy, Research Funding; *AbbVie:* Consultancy; *Bristol Myers Squibb:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: travel support; medical writing support, Research Funding; *Amgen:* Consultancy, Research Funding; *Merck:* Research Funding; *Jazz:* Consultancy, Honoraria, Research Funding; *Syros:* Consultancy, Honoraria, Research Funding; *Servier:* Consultancy, Honoraria, Research Funding; *Silence Therapeutics:* Consultancy, Honoraria, Research Funding; *Takeda:* Consultancy, Honoraria, Research Funding; *Celgene:* Honoraria; *MDS Foundation:* Membership on an entity's Board of Directors or advisory committees; *Fibrogen:* Research Funding; *Roche:* Research Funding; *BeiGene:* Research Funding; *BMS:* Research Funding.

Figure 1. Overall Survival by CR/mCR and MRD 1% Cut-Off Status at 6 Months



Kaplan-Meier plot of OS in patients who were MRD-positive at baseline with CR/mCR (best overall response of either CR or mCR as per investigator assessment according to modified IWG-MDS criteria) and MRD ≤1% at 6 months, CR/mCR and MRD >1% at 6 months, or without CR/mCR. MRD was calculated using highest VAF with combined BM and PB samples. BM, bone marrow; CR, complete remission; mCR, marrow CR; IWG, International Working Group; MDS, myelodysplastic syndromes; MRD, measurable residual disease; OS, overall survival; PB, peripheral blood; VAF, variant allele frequency.

Figure 2. Hazard Ratios of Clinical Endpoints by MRD Status at Different Cut-Offs



Time-varying covariate Cox model hazard ratios of clinical endpoints in all patients (N=112) who were MRD-positive at baseline at different MRD cut-offs. MRD was calculated at each visit using highest VAF with combined BM and PB samples. Bars represent 95% confidence intervals. BM, bone marrow; MRD, measurable residual disease; OS, overall survival; PB, peripheral blood; PFS, progression-free survival; VAF, variant allele frequency.

Figure 1

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