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The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Validation of the Composite Complete Response (cCR) Definitions in the International Working Group (IWG) 2023 Criteria in Patients (Pts) with Higher-Risk Myelodysplastic Syndromes/Neoplasms (HR-MDS) Treated with Hypomethylating Agents (HMA) - a Large, Multicenter, Retrospective Analysis from the Validate Database

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Introduction: Efficacy of therapies used in HR-MDS pts has long been assessed using IWG 2006 MDS criteria, but important limitations in clinical utility and practical application of these criteria have become apparent. The revised IWG response criteria for HR-MDS were proposed in 2023 (Zeidan et al., Blood 2023) were proposed to address these gaps. IWG 2023 re-defined CR by lowering hemoglobin (Hb) threshold from 11 to 10 g/dL and bone marrow [BM] blasts from ≤5% to <5%. Further, CR with partial hematologic recovery (CRh; <5% BM blasts, no Hb threshold, platelets ≥50 × 10^9/L; neutrophils ≥0.5 × 10^9/L; peripheral blood [PB] blasts 0%), CR with limited count recovery (CR-L; <5% BM and 0% PB blasts + PB parameters for CR met in 1 [CRuni] or 2 lineages [CRbi]), and CR equivalent (CRequ; defined for pts with baseline BM of <5%.) were all proposed as provisional endpoints. Per IWG 2023 hierarchical response assessment, if a pt met criteria for both CR-L and CRh, they would be recorded as CR-L. We sought to validate the IWG 2023 definitions of cCR (CR+CR-L+CRh+CRequ) in a large, multi-center dataset of HR-MDS pts who received HMAs.

Methods: The VALIDATE database includes HR-MDS pts treated with HMA-based therapies in frontline setting from 14 specialized centers. HR-MDS was defined as IPSS ≥1.5 or IPSS-R >3.5 (n=213 pts excluded). Pts were excluded (N=90) if age at diagnosis was <18 years, BM blasts ≥20% or unknown at HMA initiation, or if survival status, follow-up time, HMA type or initiation date were unknown. To preserve validity of response assessments, pts also were excluded (N=290) if no BM evaluation was performed or if first BM assessment was >180 days after HMA initiation, except in cases of overt disease progression. Best responses were assessed based on IWG 2006 and 2023 criteria. Kaplan-Meier analysis estimated OS from HMA initiation, and the log-rank test was used to compare subgroups. Cox multivariable regression models identified predictors of OS. This study was supported by an independent research grant from AbbVie.

Results: Of 1,223 pts in VALIDATE database, 629 were met eligibility. Median age was 68 years, 27.7% and 27.4% were red blood cell and platelet transfusion-dependent, respectively, 38.1% had *TP53* mutations, and 45.3% underwent allogeneic transplantation (allo-HCT). Most pts (71.6%) received HMA monotherapy (51.7% azacitidine, 19.9% decitabine), while 28.4% received HMA-based combinations. Median duration of therapy was 4 cycles (Range: 1-94). Median OS of different subgroups pts are shown in **Figure 1**. Median OS for pts with IWG 2023-defined cCR (CR+CR-L+CRh+CRequ; N = 230) was 26.5 months (mo; 95% CI: 20.7 - 32.2 mo) vs 14.3 mo (95% CI: 12.5 - 16.9 mo) for pts who did not achieve cCR (p=0.002). Median OS for pts who achieved IWG 2023-defined CR (N = 90) was 29.8 (95% CI: 23.1 - 41.8) vs. 26.4 mo (95% CI: 22.0 - 41.3) for IWG 2006-defined CR (p=0.71). The 124 pts (19.7%) who achieved CR-L had a median OS of 26.4 mo (95% CI: 17.6 - 36.2 mo); of those 67 pts achieved CRbi and had a median OS of 29.1 mo (95% CI: 20.7 - not reached), while 57 pts achieved CRuni and had a median OS of 18.7 mo (95% CI: 15.5 - 54.4 mo), with no significant difference in OS between CRbi and CRuni (Hazard ratio: 1.24; 95% CI: 0.78-1.98, p=0.71). Given the hierarchical prioritization of CR-L designation over CRh in IWG 2023 if a pt meets both response definitions, only 6 pts achieved CRh which precluded a reliable estimate of their OS. Similarly, CRequ was achieved only in 10 pts limiting a reliable assessment of OS in these pts. In a multivariable Cox model that adjusted for sex, HMA type, age, allo-HCT, complex karyotype, *TP53* mutation, and IPSS-M risk group, achieving a cCR per IWG 2023 criteria was statistically significantly associated with improved OS was associated with improved OS compared to those who did not achieve cCR (HR: 1.64; 95% CI: 1.30 - 2.08; p<0.001, **Figure 2**).

Discussion: In this real-world analysis of HR-MDS pts treated with HMA-based therapy, cCR according to IWG 2023 were associated improved OS. In particular, CR and CRL (including CRbi and CR uni) were associated with improved OS, supporting their inclusion in the overall response rate in clinical trials. The number of pts who achieved CRh and CRequ was too small to reliably assess their specific association with OS. Additional pts are being added to the database and detailed analyses will be presented in the meeting.

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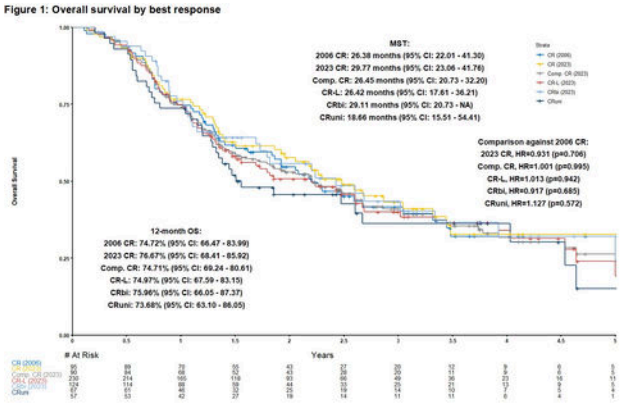

Figure 1: Overall survival by best response was compared using log-rank test. Composite CR was defined as CR + CR-L + CRh + CRequ; CR – complete remission, CR-L – complete remission with limited hematologic recovery, CRbi – CR with bilineage recovery; CRuni – CR with unilineage recovery; MST – median survival time

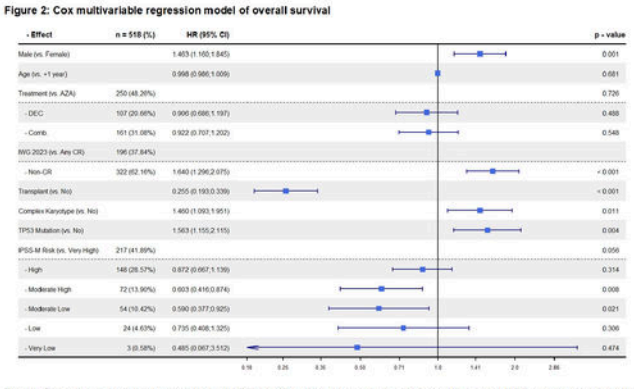

Figure: Forrest plot of variables associated with OS in multivariable regression model among higher risk MDS patients. Hazard ratio for death is shown with 95% CIs. Patients were also excluded if molecular data or information on allo-HCT and follow up were not available. AZA – azacitidine, CI – confidence interval, DEC – decitabine, HR – hazard ratio, IPSS-M – molecular international prognostic scoring system

Figure 1

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