Abstract: P786

Title: VALIDATION OF IWG-2023 RESPONSE CRITERIA, EXPANSION TO INCLUDE ALL MDS/CMML/AML PATIENTS TREATED WITH AZACITIDINE, AND COMPARISON WITH IWG-2006 AND ELN-2022 CRITERIA USING A CPH DEEP NEURAL NETWORK

Abstract Type: Poster Presentation

Topic: Myelodysplastic syndromes - Clinical

Background:

MDS, CMML and AML demonstrate considerable biologic, phenotypic, genetic and clinical overlap, and are often treated similarly. Numerous response criteria based mainly on expert opinions were published for patients (pts) with MDS (Cheson BD, Blood 2001, 2006; Platzbecker U, Blood 2019), MDS/MPN (Savona MR, Blood 2015), higher-risk (HR) MDS (Zeidan A, Blood 2023) and AML (Cheson BD, JCO 2003; Döhner H, Blood 2017 and 2022). This results in various definitions of response and disease progression, not only across the MDS/CMML/AML disease continuum, but also within different risk categories of the same entity.

While the 2023 International Working Group (IWG23) response criteria were proposed specifically for HR-MDS, they aimed to adapt (lowering of hb threshold from <11 to <10 g/dL), simplify (elimination of the categories stable disease and marrow complete remission (CR)), and potentially to set the stage for harmonization of response assessment (new compisite CR (cCR) incorporating CR/CRbi/uni/h, similar to those used in AML).

Aims:

To analyse and compare the IWG23 with IWG06 and European LeukemiaNet 2022 (ELN22) response criteria.

Methods:

Time-to-event endpoints overall survival (OS) and time to next treatment (TTNT) were analysed using the Kaplan-Meier method, after adjusting for 17 baseline parameters using Cox proportional hazards (CPH) models with SAS®9.4. Permutation-based feature importances for DeepSurv, a CPH neural network, were used to assess whether “IWG06-CR”, “IWG23-cCR” or “ELN22-CR/i/p/h” has greater predictive value. After 5-fold crossvalidation and stratification by sex, age </≥75 years and diagnosis (MDS/CMML/AML), validation C-index pairs were compared by Wilcoxon signed-rank test as described previously (Pleyer L, AJH 2023). Bonferroni-correction for multiple testing was performed.

Results:

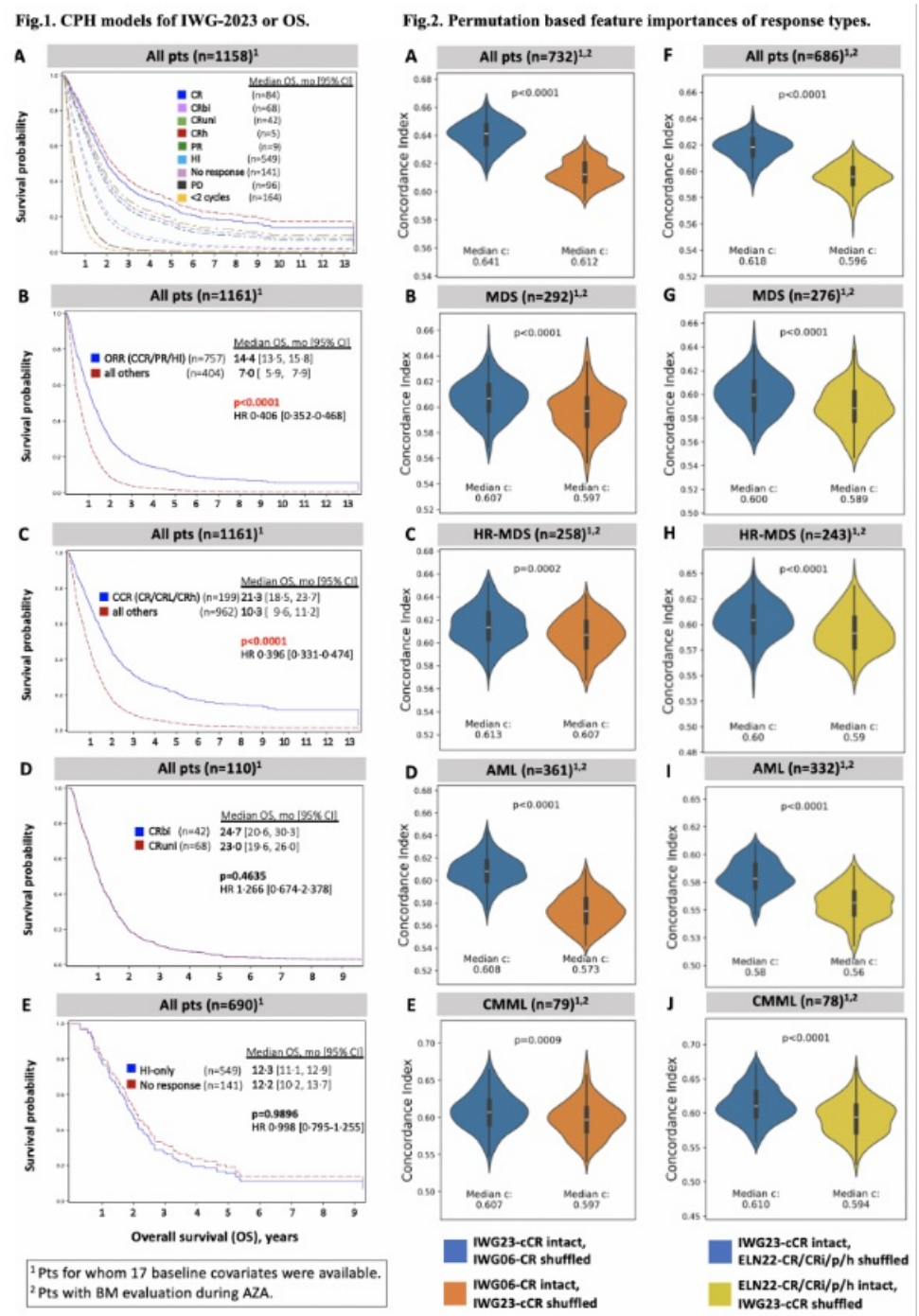
1441 pts receiving 13971 cycles of azacitidine (AZA) within the Austrian Myeloid Registry (NCT04438889) were included. After adjusting for 17 baseline covariates, median OS of 757 pts achieving ORR (cCR/PR/HI) vs those that did not was 14.4 vs 7.0 mo ($p<0.0001$, HR 0.406; Fig1B); median OS of 199 pts achieving cCR vs those that did not was 21.3 vs 10.3 mo ($p<0.0001$, HR 0.396; Fig1C); median OS of pts with CRbi vs CRuni (24.7 vs 23.0 mo, $p=0.46$; Fig1D) and hematologic improvement (HI) vs no response (12.3 vs 12.2 mo, $p=0.99$; Fig 1E) was similar, respectively. This held true for all endpoints and all (sub)diagnoses analysed separately, and also after restricting analyses to pts with a bone marrow evaluation during AZA trt.

After Bonferroni correction, 1000 random permutations of IWG23 cCR resulted in significantly ($p<0.0001$) higher performance loss than random permutations of IWG06-CR (Fig2A-E) or ELN22-CR/CRi/p/h (Fig2F-K), indicating that IWG23-cCR has more information content than the other response types. This was valid for the endpoints OS and TTNT and all (sub)diagnoses analysed.

Summary/Conclusion: In this prospective cohort study of 1441 AZA treated pts, our data confirm IWG23-cCR to be a valid and useful clinical endpoint and that outcomes of pts with CRbi/uni are similar (Bewersdorf JP, ASH2023 #324). While definitions of HI may not be optimal yet, clinical usefullness of IWG23 criteria is not

limited to HR-MDS, but can be expanded to include all MDS/CMML/AML pts treated with AZA.

Deep neural network analysis-based findings indicate that IWG23-cCR is superior to IWG06-CR and ELN22-CR/CRi/p/h at predicting pt outcomes. If these findings hold true for other trts, harmonisation and further simplification of response criteria among disease entities treated similarly, would be desirable.



Keywords: Real world data, Machine learning, Complete remission, Clinical outcome