ELSEVIER

Blood 142 (2023) 4607–4611

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Evaluation of the Molecular International Prognostic Scoring System (IPSS-M) in Patients (Pts) with Myelodysplastic Syndromes/Neoplasms (MDS) with Missing Molecular Data

Tariq Kewan, MBBChir[1], Jan Philipp Bewersdorf, MD[2], Ondrej Blaha, PhD[3], Maximilian Stahl, MD[4], Najla H Al Ali, MS[5], Amy E. DeZern, MDMHS[6], Mikkael A. Sekeres, MD[7], Hetty E. Carraway, MDMBA[8], Pinkal Desai, MD MPH[9], Elizabeth A. Griffiths, MD[10], Eytan M. Stein, MD[11], Andrew M. Brunner, MD[12], Maria L Amaya, MDPhD[13], Joshua F. Zeidner, MD[14], Michael R. Savona, MD[15], Jessica M. Stempel, MD[16], Namrata Sonia Chandhok, MD[17], Constantine Logothetis, MD[18], Hunter Cochran, MD[19], Abhay Singh, MD MPH[20], Gail J. Roboz, MD[21], Benjamin Rolles, MD[22], Eunice S. Wang, MD[23], Amyah C. Harris[24], Rory M. Shallis, MD[25], Zhuoer Xie, MDMS[5], Eric Padron, MD[5], David A Sallman, MD[26], Jaroslaw P. Maciejewski, MD, PhD, FACP[27], Matteo Giovanni Della Porta, MD[28], Rami S. Komrokji, MD[5], Amer M. Zeidan, MBBS, MHS[16]

[1] Section of Hematology, Department of Internal Medicine, Yale School of Medicine and Yale Cancer Center, New Haven, CT
[2] Memorial Sloan Kettering Cancer Center, New York, NY
[3] Yale Cancer Center, Yale University, New Haven
[4] Dana Farber Institute, Boston, MA
[5] Department of Malignant Hematology, Moffitt Cancer Center, Tampa, FL
[6] Sidney Kimmel CCC, Johns Hopkins University, Baltimore, MD
[7] Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL
[8] Department of Hematology and Medical Oncology, Taussig Cancer institute, Leukemia Program, Cleveland Clinic, Cleveland, OH
[9] Weill Cornell Medicine, The New York Presbyterian Hospital, New York, NY
[10] Leukemia Service, Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY
[11] Leukemia Service, Memorial Sloan Kettering Cancer Center, New York, NY
[12] Division of Hematology/Oncology, Dana-Farber Cancer Institute, Boston, MA
[13] Division of Hematology, University of Colorado, Aurora, CO
[14] University of North Carolina, Lineberger Comprehensive Cancer Center, Chapel Hill, NC
[15] Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN
[16] Section of Hematology, Department of Internal Medicine, Yale University School of Medicine - Yale Cancer Center, New Haven, CT
[17] University of Miami, Miami, FL
[18] Washington University, Saint Louis, MO
[19] Washington University in St. Louis, Saint Louis, MO
[20] Taussig cancer center, Cleveland Clinic, Cleveland Clinic, Cleveland, OH
[21] Weill Cornell Medicine and The New York Presbyterian Hospital, New York, NY
[22] Division of Hematology, Department of Medicine, Brigham and Women's Hospital/Harvard Medical School, Boston, MA
[23] Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY
[24] Dana Farber Cancer Institute, Boston, MA
[25] Section of Hematology, Department of Internal Medicine, Yale School of Medicine and Yale Cancer Center, Killingworth, CT
[26] H. Lee Moffitt Cancer Center, Tampa, FL
[27] Department of Translational Hematology and Oncology Research, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH
[28] Humanitas Clinical and Research Center, IRCCS, Rozzano, Italy

TK and JPB Co first; RK and AMZ are Co senior authors.

Introduction

The IPSSM incorporates molecular features to improve outcome prediction for pts with MDS. However, IPSSM requires assessment of 31 genetic mutations to classify pts into 6 risk groups. Importantly, IPSSM accounts for missing data and provides best, average, and worst IPSSM scores. Here, we used a large cohort of pts with MDS to analyze the performance of IPSSM if molecular data were missing to better understand the performance of the tool in this frequently encountered clinical setting.

Methods

For this study, we combined data from a publicly available dataset (Kewan et al. 2023 Nat com) with our multicenter VALIDATE database to increase sample size. Only pts with available molecular data were included and IPSSM was calculated twice: a. using *TP53* mutation (*TP53* ^{MT}) only and assuming that all other molecular mutations are missing (missing molecular data [IPSSM ^{MM}]) and b. using the full molecular panel (available molecular data [IPSSM ^{AM}]). *TP53* ^{MT} were included in all IPSSM calculations given frequency and significant impact on survival. Time-to-event analysis from the time of diagnosis was conducted using Kaplan-Meier estimator. The performance of different scores was evaluated by Harrell's c-index. This study was supported by an independent research grant from AbbVie.

Results

Of 2,789 pts, 2,489 had molecular data and were included. Median age was 72 years (IQR: 65-78). MDS with excess blast 1/2 (42%) was the most common subtype. Overall, 39% of pts treated with HMA and 15% of underwent transplantation. In total, 16% of pts had complex karyotypes. The most prevalent mutations were *SF3B1* (21%), *ASXL1* (20%), *TP53* (15%), *SRSF2* (15%), *DNMT3A* (12%), and *RUNX1* (10%), 39% of the pts had >1 gene mutation.

Based on IPSSR, pts were classified as very low (13%), low (47%), intermediate (13%), high (13%), and very high (14%) risk. First, we calculated IPSSM score assuming that all molecular data were missing (IPSSM ^{MM}) except *TP53* ^{MT}. Accordingly, pts were classified as very low (4%), low (33%), moderate low (19%), moderate high (14%), high (17%), and very high (14%) risk. IPSSM ^{MM} resulted in the re-stratification of 1623 (66%) pts of which 1104 (68%) pts were up-staged, and 519 (32%) pts were down-staged. When applying actual molecular data (IPSS-M ^{AM}), pts were classified as very low (14%), low (30%), moderate low (12%), moderate high (10%), high (17%), and very high (17%) risk. When compared with IPSSR, IPSSM ^{AM} resulted in re-stratification of 1218 pts (50%) of which 868 pts (71%) were upstaged (**Panel A**). When comparing IPSSM ^{MM} with IPSSM ^{AM}, 1243 pts (51%) were assigned to the same risk group and 1186 pts (49%) were assigned to different risk groups. Amongst reclassified pts, 431 (36%) were upstaged and 755 (64%) were down staged. Only 109 pts (5%) were reclassified with more than one shift.

Median follow-up time was 24 (IQR:10-77) months (mo) with a median overall survival (OS) of 50 mo (95% CI: 47-55). The probability of OS based on IPSSM ^{MM} and IPSSM ^{AM} risk groups was significantly different (p-value: <0.0001 for both), **Panel B**. Median OS (mo) based on IPSSM ^{MM} vs. IPSSM ^{AM} were as follows: very low (not reached vs. 125), low (103 vs. 82), moderate low (63 vs. 58), moderate high (46 vs. 43), high (27 vs. 24), and very high (13 vs.15). Median OS based on IPSSR were: very low (not reached), low (78), intermediate (36), high (24), and very high (14). The median LFS (n=1100 pts) based on IPSSM ^{MM} vs. IPSSM ^{AM} were as follows: very low (41 vs. 78), low (63 vs. 54), moderate low (39 vs. 33), moderate high (26 vs. 29), high (18 vs. 15), and very high (11 vs. 13).

IPSSM ^{MM} showed comparable performance to IPSSM ^{AM} with c-index (95%CI): 0.713 (0.697 -0.728) vs. 0.714 (0.699-0.729) for OS and 0.645 (0.622-0.669) vs. 0.623 (0.599-0.647) for LFS. When used as continuous scores, IPSSM ^{MM} continues to be comparable to IPSSM ^{AM} for OS (c-index:0.721 vs. 0.730) and LFS (c-index:0.655 vs. 0.641). IPSS-R had a lower c-index for OS (0.688) and LFS (0.622).

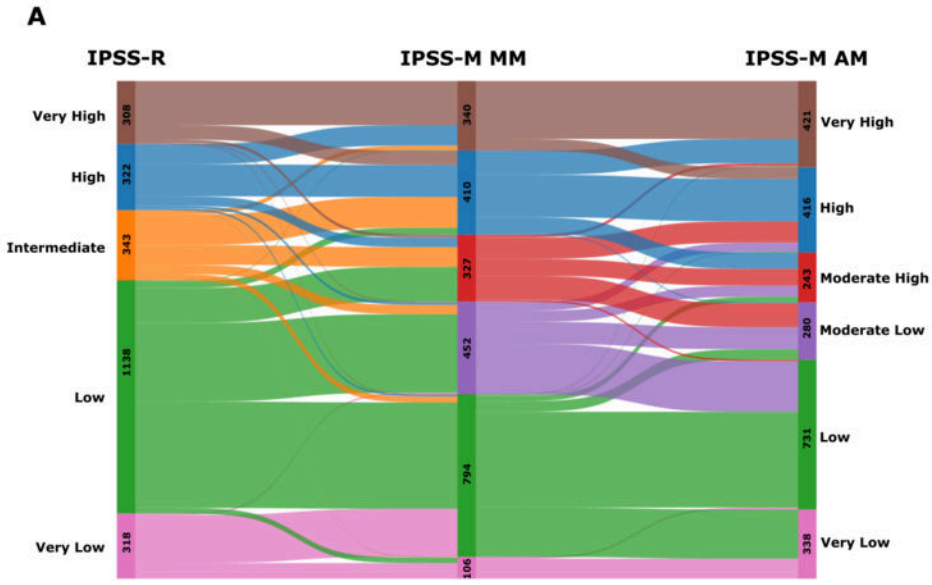
Conclusions

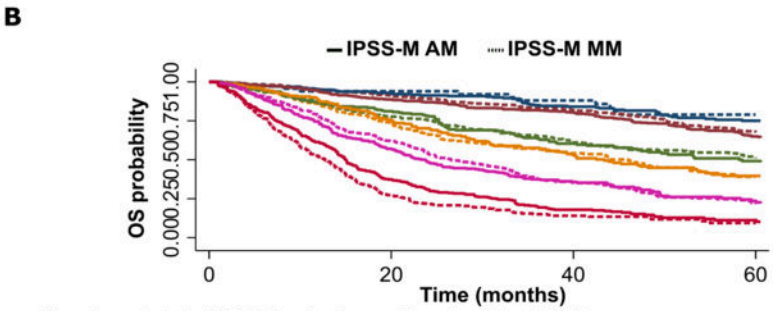
Our study supports prognostic and clinical value of IPSSM even if most molecular data are missing, confirming that IPSSM adjusts well for missing molecular data and can be used in clinical practice if molecular data are largely missing. While molecular testing remains optimal for accurate risk stratification in MDS, our data suggest that clinical, pathological and cytogenetic data continue to be the main determinant of outcome prediction for pts with MDS.

Disclosures Stahl: *Kymera:* Membership on an entity's Board of Directors or advisory committees; *Rigel:* Membership on an entity's Board of Directors or advisory committees; *GSK:* Membership on an entity's Board of Directors or advisory committees; *Dedham group:* Consultancy; *Haymarket Media:* Other: GME activity ; *Clinical care options:* Other: GME activity ; *Novartis:* Membership on an entity's Board of Directors or advisory committees, Other: GME activity ; *Boston Consulting:* Consultancy; *Curis Oncology:* Other: GME activity ; *Sierra Oncology:* Membership on an entity's Board of Directors or advisory committees. **DeZern:** *Sobi:* Consultancy; *Novartis:* Membership on an entity's Board of Directors or advisory committees; *Geron:* Membership on an entity's Board of Directors or advisory committees; *Caribou:* Membership on an entity's Board of Directors or advisory committees; *Bristol Myers Squibb:* Consultancy; *Appellis:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **Sekeres:** *Geron:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Kurome:* Consultancy, Current holder of *stock options* in a privately-held company; *BMS:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **Carraway:** *AbbVie:* Other; *Stemline Therapeutics:* Consultancy, Speakers Bureau; *BMS:* Consultancy, Research Funding, Speakers Bureau; *Novartis:* Consultancy, Other: Travel, Accommodations, Expenses , Speakers Bureau; *Astex Pharmaceuticals:* Other; *Agios:* Consultancy, Speakers Bureau; *Jazz Pharmaceuticals:* Consultancy, Other: Travel, Accommodations, Expenses , Speakers Bureau; *Daiichi:* Consultancy; *Syndax:* Other: DSMB; *Takeda:* Other; *Celgene:* Research Funding; *Genentech:* Consultancy. **Desai:** *BMS:* Consultancy, Other: Advisory role; *Servier:* Consultancy, Other: Ad-

visory role; *Janssen Research & Development:* Research Funding; *Janssen Pharmaceuticals:* Current Employment; *Abbvie:* Consultancy, Other: Advisory role. **Griffiths:** *CTI Biopharma:* Consultancy; *Novartis:* Consultancy, Research Funding; *Physicians Educational Resource:* Honoraria; *S. Karger Publishing:* Honoraria; *Genentech, Inc.:* Consultancy, Research Funding; *AAMDSIF:* Honoraria; *MDS International Foundation:* Honoraria; *Blueprint Medicines, Inc:* Research Funding; *Astex Pharmaceuticals:* Research Funding; *Celldex Therapeutics:* Research Funding; *American Society of Hematology:* Honoraria; *Abbvie:* Consultancy; *Takeda Oncology:* Consultancy; *Bristol Myers Squibb:* Consultancy, Research Funding; *Picnic Health:* Membership on an entity's Board of Directors or advisory committees; *Taiho Oncology:* Consultancy; *Artis Ventures:* Membership on an entity's Board of Directors or advisory committees; *MediCom Worldwide, Inc.:* Honoraria; *Alexion Pharmaceuticals:* Consultancy, Research Funding; *Apellis Pharmaceuticals:* Consultancy, Research Funding; *NextCure, Inc:* Research Funding; *Partner Therapeutics:* Consultancy; *AstraZeneca Rare Disease:* Consultancy, Research Funding; *Medscape:* Honoraria; *Vera and Joseph Dresner Foundation:* Membership on an entity's Board of Directors or advisory committees. **Stein:** *Novartis:* Consultancy; *Bristol Myers Squib:* Consultancy, Research Funding; *Eisai:* Research Funding; *PinotBio:* Consultancy; *Janssen:* Consultancy; *Abbvie:* Consultancy; *Genesis:* Consultancy; *Genentech:* Consultancy; *Agios:* Consultancy; *Jazz:* Consultancy; *Menarini:* Consultancy; *Daiichi:* Consultancy; *Aptose:* Consultancy; *Neoleukin:* Consultancy; *Gilead:* Consultancy; *Syndax:* Consultancy; *Foghorn:* Consultancy; *CTI Biopharma:* Consultancy; *OnCusp:* Consultancy; *Calithera:* Consultancy; *Servier:* Consultancy; *Syros:* Consultancy; *Astellas:* Consultancy; *Ono Pharma:* Consultancy; *Blueprint:* Consultancy. **Brunner:** *Agios:* Consultancy, Research Funding; *Acceleron:* Consultancy; *AstraZeneca:* Research Funding; *Celgene/BMS:* Consultancy, Research Funding; *GSK:* Research Funding; *Gilead:* Consultancy; *Taiho:* Consultancy; *Janssen:* Research Funding; *Keros Therapeutics:* Consultancy; *Takeda:* Consultancy; *Novartis:* Consultancy, Research Funding. **Zeidner:** *Astex:* Research Funding; *Arog:* Research Funding; *AbbVie:* Consultancy, Honoraria, Research Funding; *Daiichi Sankyo:* Honoraria; *Gilead:* Consultancy, Honoraria, Research Funding; *Foghorn:* Consultancy; *Immunogen:* Honoraria; *Takeda:* Research Funding; *Sumitomo Dainippon Pharma:* Research Funding; *Stemline:* Research Funding; *Shattuck Labs:* Honoraria, Research Funding; *Servier:* Consultancy, Honoraria; *Sellas:* Consultancy; *Novartis:* Consultancy; *Merck:* Research Funding; *Jazz:* Research Funding. **Savona:** *Geron Corporation:* Membership on an entity's Board of Directors or advisory committees; *Forma Therapeutics Inc.:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *AbbVie Inc.:* Membership on an entity's Board of Directors or advisory committees; *Ryvu Therapeutics:* Consultancy, Current equity holder in publicly-traded company, Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees; *Karyopharm Therapeutics Inc.:* Consultancy, Current equity holder in publicly-traded company, Membership on an entity's Board of Directors or advisory committees; *CTI BioPharma Corp.:* Membership on an entity's Board of Directors or advisory committees; *Bristol Myers Squibb:* Membership on an entity's Board of Directors or advisory committees; *Sierra Oncology, Inc.:* Membership on an entity's Board of Directors or advisory committees; *Taiho:* Membership on an entity's Board of Directors or advisory committees; *Takeda Pharmaceutical Company:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *TG Therapeutics, Inc.:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Boehringer Ingelheim:* Patents & Royalties; *ALX Oncology:* Research Funding; *Astex Pharmaceuticals:* Research Funding; *Incyte Corporation:* Research Funding. **Singh:** *Rigel:* Other: Advisor or review panel participant. **Roboz:** *AbbVie:* Consultancy; *Amgen:* Consultancy; *Actinium:* Consultancy; *BMS:* Consultancy; *Astellas:* Consultancy; *Agios:* Consultancy; *Blueprint:* Consultancy; *AZ:* Consultancy; *Bluebird bio:* Consultancy; *GSK:* Consultancy; *Janssen:* Consultancy, Research Funding; *Mesoblast:* Consultancy; *MEI:* Consultancy; *Jazz:* Consultancy; *Jasper:* Consultancy; *Novartis:* Consultancy; *Pfizer:* Consultancy; *Syndax:* Consultancy; *Takeda:* Consultancy. **Wang:** *GlaxoSmithKline:* Consultancy; *Jazz:* Consultancy; *Kite:* Consultancy, Speakers Bureau; *Novartis:* Consultancy, Speakers Bureau; *Pfizer:* Consultancy, Speakers Bureau; *PharmaEssentia:* Consultancy; *Takeda:* Consultancy; *Dava oncology:* Speakers Bureau; *Kura Oncology:* Speakers Bureau; *Gilead:* Consultancy; *BMS:* Consultancy; *Astellas:* Consultancy, Speakers Bureau; *Abbvie:* Consultancy. **Shallis:** *Servier:* Consultancy; *Bristol Myers Squibb:* Consultancy; *Gilead Sciences:* Consultancy; *Curio Science:* Consultancy; *Rigel:* Consultancy. **Padron:** *Incyte:* Research Funding; *BMS:* Research Funding; *Gillead:* Membership on an entity's Board of Directors or advisory committees; *CTI:* Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Membership on an entity's Board of Directors or advisory committees; *Pharmaessentia:* Membership on an entity's Board of Directors or advisory committees; *Kura:* Research Funding. **Sallman:** *Aprea, Jazz:* Research Funding; *AbbVie, Affimed Gmbh, Gilead, Incyte, Intellisphere, LLC, Molecular Partners AG, PGEN Therapeutics, Inc., Takeda, Zentalis; Advisory board for AvenCell, BlueBird Bio, BMS, Intellia, Jasper Therapeutics, Kite, Magenta Therapeutics, NKARTA, Novartis, Orbita:* Consultancy. **Maciejewski:** *Novartis:* Honoraria, Speakers Bureau; *Alexion:* Membership on an entity's Board of Directors or advisory committees; *Regeneron:* Consultancy, Honoraria; *Omeros:* Consultancy. **Della Porta:** *Bristol Myers Squibb:* Honoraria, Membership on an entity's Board of Directors or advisory committees. **Komrokji:** *BMS:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *AbbVie, CTI biopharma, Jazz, Pharma Essentia, Servio:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Rigel, Taiho, DSI:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees; *Geron:* Consultancy. **Zeidan:** *Kura:* Consultancy, Honoraria; *Astellas:* Consultancy, Honoraria; *Astex:* Research Funding; *Foran:* Consultancy, Research Funding; *Syros:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria; *Schrödinger:* Consultancy, Honoraria; *Regeneron:* Consultancy, Honoraria; *BeyondSpring:* Consultancy, Honoraria; *Chiesi:* Consultancy, Honoraria; *Syndax:* Consultancy, Honoraria; *Takeda:* Consultancy, Honoraria; *Notable:* Consultancy, Honoraria; *Gilead:* Consultancy, Honoraria; *Epizyme:* Consultancy, Honoraria; *Genentech:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria; *Amgen:* Consultancy, Honoraria; *Otsuka:* Consultancy, Honoraria; *Ionis:* Consultancy, Honoraria; *Lox Oncology:* Consultancy, Honoraria; *Tyme:* Consultancy, Honoraria;

Incyte: Consultancy, Honoraria; *Shattuck Labs:* Research Funding; *ALX Oncology:* Consultancy, Honoraria; *BioCryst:* Consultancy, Honoraria; *Mendus:* Consultancy, Honoraria; *Seattle Genetics:* Consultancy, Honoraria; *Orum:* Consultancy, Honoraria; *Taiho:* Consultancy, Honoraria; *Geron:* Consultancy, Honoraria; *Daiichi Sankyo:* Consultancy, Honoraria; *Agios:* Consultancy, Honoraria; *Boehringer-Ingelheim:* Consultancy, Honoraria; *Servier:* Consultancy, Honoraria; *Jazz:* Consultancy, Honoraria; *Celgene/BMS:* Consultancy, Honoraria; *Pfizer:* Consultancy, Honoraria; *AbbVie:* Consultancy, Honoraria; *Zentalis:* Consultancy, Honoraria.





Number at risk (IPSS-M missing molecular data [MM])

Very Low	75	53	39	26
Low	739	569	410	246
Moderate Low	428	281	172	95
Moderate High	310	191	103	52
High	396	208	88	35
Very High	332	72	25	5

Number at risk (IPSS-M available molecular data [AM])

Very Low	293	229	174	112
Low	679	513	370	217
Moderate Low	265	179	94	54
Moderate High	233	142	76	40
High	398	184	77	26
Very High	412	127	46	10

A. Distribution of patients (n=2,489) based on International Prognostic Scoring System-Revised (IPSS-R), International Molecular Prognostic Scoring System with missing molecular data (IPSS-M MM), and International Molecular Prognostic Scoring System with available molecular data (IPSS-M AM)

B. Kaplan-Meier probability estimate of overall survival (OS) for patients stratified by International Molecular Prognostic Scoring System with missing molecular data (IPSS-M MM) and International Molecular Prognostic Scoring System with available molecular data (IPSS-M AM)

Figure 1

https://doi.org/10.1182/blood-2023-187053