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POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Combining Gene Mutation with Transcriptomic Data Improves Outcome Prediction in Myelodysplastic Syndromes

Elisabetta Sauta, PhD[1], Matteo Zampini, PhD[1], Daniele Dall'Olio, PhD[2], Claudia Sala, PhD[2], Gabriele Todisco, MD[1], Erica Travaglino, BS[1], Luca Lanino, MD[3], Cristina Astrid Tentori, MD[1], Giulia Maggioni, MD[1], Saverio D'Amico, MSc[1], Gianluca Asti, MSc[1], Lorenzo Dall'Olio, PhD[4], Ettore Mosca, PhD[5], Marta Ubezio, MD[1], Alessia Campagna, MD[1], Elena Riva, BSc[1], Marilena Bicchieri, PhD[1], Victor Savevski, MEng[1], Armando Santoro, MD[6,7], Shahram Kordasti, MDPhD[8], Valeria Santini, MD[9], Maria Diez-Campelo, MD PhD[10], Anne Sophie Kubasch, MD[11], Uwe Platzbecker, MD[12], Pierre Fenaux, MD PhD[13], Lin Pierre Zhao, MD[13], Amer M. Zeidan, MBBS, MHS[14], Torsten Haferlach, MD PhD[15], Gastone Castellani, PhD[2], Matteo Giovanni Della Porta, MD[1,16]

[1] Humanitas Clinical and Research Center, IRCCS, Rozzano, Italy
[2] University of Bologna, Bologna, Italy
[3] Humanitas Clinical and Research Center, IRCCS, Rozzano, Italy
[4] Data Science and Bioinformatics Laboratory, IRCCS Institute of Neurological Sciences of Bologna, Bologna, Italy
[5] Institute of Biomedical Technologies, National Research Council (CNR), Segrate, ITA
[6] Humanitas Cancer Center, Rozzano, Italy
[7] Humanitas University, Pieve Emanuele and IRCCS Humanitas Research Hospital- Humanitas Cancer Center Rozzano, Milan, Italy
[8] King's College London, London, United Kingdom
[9] MDS Unit, DMSC, AOU Careggi, University of Florence, Firenze, Italy
[10] Hospital Universitario de Salamanca, Salamanca, Spain
[11] Department of Hematology, Cellular Therapy, Hemostaseology and Infectious Diseases, University Medical Center Leipzig, Leipzig, Germany
[12] Medical Clinic and Policlinic 1, Hematology and Cellular Therapy, University Hospital Leipzig, Leipzig, Germany
[13] Saint Louis hospital APHP, Paris, France
[14] Section of Hematology, Department of Internal Medicine, Yale School of Medicine and Yale Cancer Center, New Haven, CT
[15] MLL Munich Leukemia Laboratory, Munich, Germany
[16] Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Italy

Background and Aim. Myelodysplastic syndromes (MDS) are myeloid neoplasms characterized by peripheral blood cytopenias and risk of progression to acute myeloid leukemia (AML). Disease management is challenged by heterogeneity in clinical courses and survival probability. Recently, the genomic screening integration (by Molecular International Prognostic Scoring System, IPSS-M) into patient's assessment has resulted into a significant improvement in predicting clinical outcomes compared to the conventional prognostic score (Revised IPSS, IPSS-R). Many of the consequences of genetic and cytogenetic alterations will affect gene expression by means of transcriptional and epigenetic instability and altered microenviromental signaling. The aim of this project conducted by GenoMed4All and Synthema EU consortia is to link genomic information with transcriptomic data for possibly improving the prediction of clinical outcomes in MDS patients.
*Patients and Methods.*Clinical, cytogenetic, genomic (somatic mutations screening of 31 target genes) and transcriptomic (bulk RNA-seq of CD34 $^{+}$ bone marrow cells) data were collected at diagnosis in 389 MDS patients. Transcriptomic and genomic profiles were processed and the former were normalized before Principal Component Analysis (PCA) dimensionality reduction to mine the interdependency of expression-wide perturbation and recurrent genomic alterations. The prognostic impacts of genetic, cytogenetic, transcriptomic, clinical and demographic features were assessed with a penalized Cox's proportional hazards model *[Gerstung M et al, Nat Commun. 2015. 6, 5901]* considering the Overall Survival (OS) as primary end point. A 5-fold cross-validating (CV) scheme was exploited to control bias in risk estimation. Model accuracy was assessed using Harrell's concordance index (C-index). An independent validation of the results on 202 patients was planned.

*Results.*We first processed each data layer assessing data robustness, removed not informative variables and scaled quantitative ones. We considered recurrent genomic and cytogenetic lesions (present in ≥5 patients), platelets, hemoglobin and bone marrow blasts (%), age and sex as covariates. To explore the main patterns of expression changes, PCA was performed to reduce multidimensional correlated expression features (20 PCs was selected, explaining 42% of the total transcriptomic variability). To evaluate the prognostic power of each data layer we grouped all available features into five groups: gene mutations (n=15), cytogenetic alterations (n=7), expression data (n=20), blood counts (n=3) and demographic variables (n=2). Within a 5-fold CV we combined these variables in our integrative model to calculate MDS patients risk. The obtained predictive accuracy (C-index) for OS was 0.83, underlying that transcriptomic data significantly improved the current standard prognostic scoring systems. Accordingly, in our patient population, the C-index of the conventional IPSS-R score and the new IPSS-M were 0.68 and 0.76, respectively. A similar improvement by adding transcriptomic data was observed in prediction of the risk of AML evolution. Moreover, by analyzing the contribution of each feature category to the OS probability (*Figure 1*), in term of explained variance, the relative impact of transcriptomic is 40%, with the remaining prognostic information distributed among genomic features (somatic gene mutations and cytogenetics lesions, 24%), demographics (20%) and clinical features (15%). An independent validation of these results on 202 patients is currently ongoing.

Figure 2 shows an example of personalized survival prediction using patients from the study population. In two subjects with same clinical phenotype and mutations leading to a similar IPSS-M prognosis, the integrative model captures additional prognostic information and efficiently predicts clinical outcome. Given the complexity of our model, specific technological support is needed to combine data at individual patient level and to translate it into a personalized outcome prediction. To this aim, we created a prototype web portal based on our dataset for user-defined genomic/transcriptomic and clinical features.

Conclusion. In predicting survival of MDS patients, genomic, transcriptomic and diagnostic clinical variables all have utility, with a significant contribution from the transcriptome.

Disclosures Santoro: *Sanofi:* Consultancy; *Incyte:* Consultancy; *BMS:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Servier:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Gilead:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Pfizer:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Eisai:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Bayer:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Merck MSD:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Takeda:* Speakers Bureau; *Roche:* Speakers Bureau; *Abbvie:* Speakers Bureau; *Amgen:* Speakers Bureau; *Celgene (BMS):* Speakers Bureau; *AstraZeneca:* Speakers Bureau; *Eli Lilly:* Speakers Bureau; *Sandoz:* Speakers Bureau; *Novartis:* Speakers Bureau; *Arqule:* Other. **Kordasti:** *MorphoSys:* Research Funding; *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Beckman Coulter:* Honoraria. **Santini:** *BMS, Abbvie, Geron, Gilead, CTI, Otsuka, servier, janssen, Syros:* Membership on an entity's Board of Directors or advisory committees. **Diez-Campelo:** *BMS/Celgene:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Advisory board fees; *Novartis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Gilead Sciences:* Other: Travel expense reimbursement; *GSK:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **Platzbecker:** *Roche:* Research Funding; *Syros:* Consultancy, Honoraria, Research Funding; *Curis:* Consultancy, Research Funding; *Servier:* Consultancy, Honoraria, Research Funding; *Amgen:* Consultancy, Research Funding; *Novartis:* Consultancy, Honoraria, Research Funding; *MDS Foundation:* Membership on an entity's Board of Directors or advisory committees; *Fibrogen:* Research Funding; *Takeda:* Consultancy, Honoraria, Research Funding; *Silence Therapeutics:* Consultancy, Honoraria, Research Funding; *BeiGene:* Research Funding; *AbbVie:* Consultancy; *Geron:* Consultancy, Research Funding; *Janssen Biotech:* Consultancy, Research Funding; *Jazz:* Consultancy, Honoraria, Research Funding; *Merck:* Research Funding; *Bristol Myers Squibb:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: travel support; medical writing support, Research Funding; *Celgene:* Honoraria; *BMS:* Research Funding. **Fenaux:** *Bristol Myers Squibb:* Consultancy, Honoraria, Research Funding; *AbbVie:* Consultancy, Honoraria, Research Funding; *Janssen:* Consultancy, Honoraria, Research Funding; *Jazz:* Consultancy, Honoraria, Research Funding; *Novartis:* Consultancy, Honoraria, Research Funding; *French MDS Group:* Honoraria. **Zeidan:** *Seattle Genetics:* Consultancy, Honoraria; *Taiho:* Consultancy, Honoraria; *Otsuka:* Consultancy, Honoraria; *BeyondSpring:* Consultancy, Honoraria; *Takeda:* Consultancy, Honoraria; *Ionis:* Consultancy, Honoraria; *Amgen:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria; *Genentech:* Consultancy, Honoraria; *Epizyme:* Consultancy, Honoraria; *Syndax:* Consultancy, Honoraria; *Gilead:* Consultancy, Honoraria; *Kura:* Consultancy, Honoraria; *Chiesi:* Consultancy, Honoraria; *ALX Oncology:* Consultancy, Honoraria; *BioCryst:* Consultancy, Honoraria; *Notable:* Consultancy, Honoraria; *Orum:* Consultancy, Honoraria; *Mendus:* Consultancy, Honoraria; *Zentalis:* Consultancy, Honoraria; *Schrödinger:* Consultancy, Honoraria; *Regeneron:* Consultancy, Honoraria; *Tyme:* Consultancy, Honoraria; *Astex:* Research Funding; *Shattuck Labs:* Research Funding; *Foran:* Consultancy, Research Funding; *Syros:* Consultancy, Honoraria; *Lox Oncology:* Consultancy, Honoraria; *Incyte:* Consultancy, Honoraria; *Servier:* Consultancy, Honoraria; *Agios:* Consultancy, Honoraria; *Boehringer-Ingelheim:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria; *Astellas:* Consultancy, Honoraria; *Daiichi Sankyo:* Consultancy, Honoraria; *Geron:* Consultancy, Honoraria; *AbbVie:* Consultancy, Honoraria; *Jazz:* Consultancy, Honoraria; *Celgene/BMS:* Consultancy, Honoraria; *Pfizer:* Consultancy, Honoraria. **Haferlach:** *MLL Munich Leukemia Laboratory:* Current Employment, Other: Equity Ownership. **Della Porta:** *Bristol Myers Squibb:* Honoraria, Membership on an entity's Board of Directors or advisory committees.

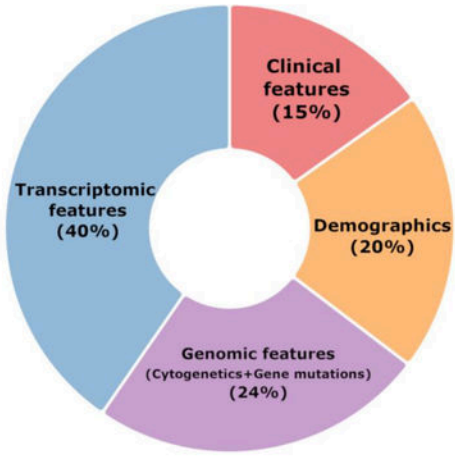

Figure 1. Distribution of risk contribution as a fraction of the explained variation related to the survival integrative model for 389 MDS patients from GenoMed4All/Synthema consortia.

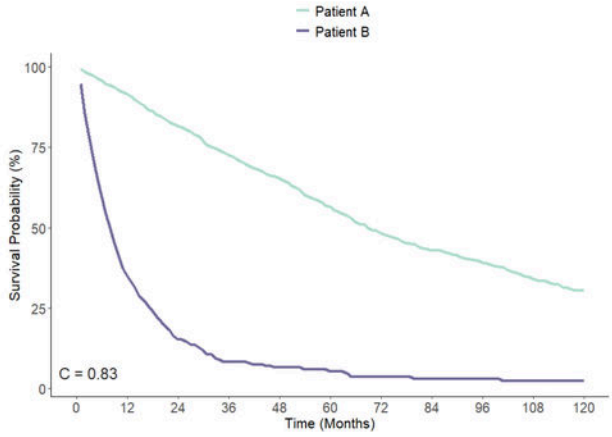

Figure 2. Personalized prediction of overall survival using a multivariate prognostic model including transcriptomic together with clinical and genomic features in two patients from the GenoMed4All/Synthema cohorts (labeled as Patient A and Patient B), both carrying *TET2* and *SRSF2* mutations who were classified as MDS with multilineage dysplasia according to 2016 WHO classification and belonging to moderate low-risk group according to IPSS-M. Using currently available prognostication including gene mutations, both patients are predicted to have an indolent clinical course without significant risk of disease evolution and death. When looking at transcriptomic profile, Patient B showed specific aberration in p53 pathways regulation in CD34+ progenitors (even in absence of a detectable *TP53* gene mutation) together with significant downregulation of HLA class II members and their master regulator CIITA, and the up-regulation of the immunosuppressive enzyme CD73 (suggesting an immunosuppressive phenotype in this patient). We then calculated expected survival by using the novel prognostic model including transcriptomic features (exponential survival curves are reported in the figure). Accordingly, the estimation of life expectancy is now significantly different in these two patients, as underlined by the slope of the two exponential curves. The model predicts a better probability of survival for Patient A with respect to Patient B, thus reflecting more precisely the observed clinical outcome. In fact, Patient B died 30 months after the diagnosis as a result of leukemic evolution, whereas Patient A was still alive without evidence of disease progression after 65 months of follow-up. IPSS-M fails to capture such a difference in clinical outcome.

Figure 1

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