S130: NPM1 mutated AML: impact of co-mutational patterns - results of the European Harmony Alliance

Hernández-Sánchez, A., Villaverde-Ramiro, Á., Martínez Elicegui, J., González, T., Benner, A., Sträng, E., Castellani, G., Heckman, C. A., Versluis, J., Abáigar, M., Sobas, M., Azibeiro, R., Tur, L., Valk, P. J., Metzeler, K. H., Ayala, R., Dall'Olio, D., Tettero, J., Martínez-López, J., ... Bullinger, L. (2022). S130: NPM1 mutated AML: impact of co-mutational patterns - results of the European Harmony Alliance. *HemaSphere*, *6*, 31-32. https://doi.org/10.1097/01.hs9.0000843412.59637.1b

Published in:
HemaSphere

Document Version:
Publisher's PDF, also known as Version of record

HemaSphere

EHA EUROPEAN HEMATOLOGY ASSOCIATION

S130 NPM1 MUTATED AML: IMPACT OF CO-MUTATIONAL PATTERNS - RESULTS OF THE EUROPEAN HARMONY ALLIANCE

Topic: 04. Acute myeloid leukemia - Clinical

Alberto Hernández-Sánchez[1, 2], Ángela Villaverde-Ramiro[2], Javier Martínez Elicegui[2], Teresa González[2, 3], Axel Benner[4], Eric Sträng[5], Gastone Castellani[6], Caroline A. Heckman[7, 8], Jurjen Versluis[9], María Abáigar[2, 3], Marta Sobas[10], Raúl Azibeiro[1, 2], Laura Tur[11], Peter JM Valk[9], Klaus H Metzeler[12], Rosa Ayala[13], Daniele Dall'Olio[6], Jesse Tettero[14], Joaquín Martínez-López[13], Hervé Dombret[15], Marta Pratcorona[16], Frederik Damm[5], Ken I Mills[17], Jiří Mayer[18], Christian Thiede[19], Maria Teresa Voso[20], Guillermo F Sanz[21, 22], Frederico Calado[23], Konstanze Döhner[24], Verena I Gaidzik[25], Michael Heuser[26], Torsten Haferlach[27], Amin T Turki[28, 29], Dirk Reinhardt[28], Rubén Villoria Medina[11], Michel van Speybroeck[30], Renate Schulze-Rath[31], Martje Barbus[32], John E Butler[33], Jesús M Hernández Rivas[1, 2, 3], Brian JP Huntly[34], Gert J Ossenkoppele[14, 35, 36], Hartmut Döhner[24], Lars Bullinger[5]

[1] Hospital Universitario de Salamanca, Salamanca, Spain;[2] Instituto de Investigación Biomédica de Salamanca (IBSAL), Salamanca, Spain;[3] Centro de Investigación del Cáncer (CIC), Salamanca, Spain;[4] German Cancer Research Center (DKFZ), Heidelberg, Germany;[5] Charité Universitätsmedizin Berlin, Berlin, Germany;[6] University of Bologna, Bologna, Italy;[7] University of Helsinki, Helsinki, Finland;[8] Institute for Molecular Medicine Finland, Helsinki, Finland;[9] Erasmus University Medical Center Cancer Institute, Rotterdam, Netherlands;[10] Wroclaw Medical University, Wroclaw, Poland;[11] GMV Innovating Solutions, Valencia, Spain;[12] University of Munich, Munich, Germany;[13] Hospital Universitario 12 de Octubre, Madrid, Spain;[14] Amsterdam University Medical Center, Amsterdam, Netherlands;[15] EA3518 Leukemia Translational Laboratory, Paris, France;[16] Hospital de la Santa Creu i Sant Pau, Barcelona, Spain;[17] Queens University Belfast, Belfast, United Kingdom;[18] University Hospital Brnoand Masaryk University, Brno, Czech Republic;[19] University of Technics Dresden Medical Dept., Dresden, Germany;[20] University of Rome "Cattolica S. Cuore", Rome, Italy;[21] Hospital Universitario y Politécnico La Fe, Valencia, Spain;[22] Instituto de Salud Carlos III (CIBERONC), Valencia, Spain;[23] Novartis, Oncology Region Europe, Basel, Switzerland;[24] University Hospital of Ulm, Ulm, Germany;[25] Ulm University Hospital, Ulm, Germany;[26] Hannover Medical School, Hannover, Germany;[27] MLL Munich Leukemia Laboratory, Munich, Germany;[28] Essen University Hospital, Essen, Germany;[29] West-German Cancer Center, Essen, Germany;[30] Janssen Pharmaceutica N.V., Beerse, Belgium;[31] Bayer Pharma AG, Berlin, Germany;[32] AbbVie Germany GmbH & Co. KG, Wiesbaden, Germany;[33] Bayer AG, Berlin, Germany;[34] Wellcome - MRC Cambridge Stem Cell Institute, Cambridge, United Kingdom;[35] VU University Medical Center, Amsterdam, Netherlands;[36] Cancer Center Amsterdam, Amsterdam, Netherlands

Background:

Acute myeloid leukemia (AML) is a heterogeneous disease in terms of clinical features, outcomes and genetics. While mutations of *NPM1* are usually considered as a favorable prognostic marker, the vast majority of the patients carry several co-mutations that might influence the prognosis. Therefore, a better understanding of the *NPM1*^{mut} AML mutational landscape is warranted. The large cohort of AML patients collected within the European HARMONY Alliance provides an excellent basis for this purpose.

Aims:

To identify clinically significant co-mutational patterns in *NPM1*^{mut} AML in order to establish a revised risk stratification model.

Methods:

From the HARMONY Alliance AML database, a total of 1001 *NPM1*^{mut} intensively treated patients were selected. Clinically significant co-mutations were evaluated using graphical patterns created with the Gephi tool and confirmed by detailed survival analysis using Kaplan-Meier and Cox regression models. Finally, a novel multi-state risk stratification model for *NPM1*^{mut} AML was established.

Abstract Book Citations: Authors, Title, HemaSphere, 2022;6:(S3):pages. The individual abstract DOIs can be found at https://journals.lww.com/hemasphere/pages/default.aspx.

Results:

The study population of 1001 *NPM1*^{mut} AML patients included 57% females and median age was 53 years. Regarding ELN2017 classification, 68% of patients were classified into the favorable, 29% intermediate and 3% adverse risk groups. The most frequent co-mutations were *DNMT3A* (54%), followed by *FLT3*-ITD (38%). In total, 24% of patients presented with a high allelic mutant-to-wildtype ratio ≥0.5 (*FLT3*-ITD^{high}) while 14% had low allelic ratio <0.5 (*FLT3*-ITD^{low}). Other frequent co-mutations were *NRAS* (21%), *TET2* (20%) and *PTPN11* (15%).

The triple mutation pattern of *NPM1*^{mut} + *FLT3*-ITD^{high} + *DNMT3A*^{mut} identified a subgroup with adverse prognosis (2-year OS of 25%), similar to *NPM1*^{mut} + *TP53*^{mut}. The combination of *FLT3*-ITD^{low} + *DNMT3A*^{mut} or *FLT3*-ITD^{high} + *DNMT3A*^{wt} was associated with intermediate prognosis (2-year OS of 45% and 53% respectively). Notably, mutations of *NRAS*, *KRAS*, *PTPN11* or *RAD21* were identified to be associated with better OS. However, in the context of *NPM1*^{mut} + *DNMT3A*^{mut} these mutations did not affect the prognosis when a *FLT3*-ITD was present. This information is summarized in a 3-category risk classification model (**Figure 1**).

The revised *NPM1*^{mut} favorable group presented with a 2-year OS of 73%, while for intermediate and adverse groups the OS was 54% and 27% respectively (p<0.001). Regarding relapse free survival (RFS), the median was not reached in the favorable group, while it was 23 months for intermediate and 6 months for adverse group (p<0.001). It should be noted that 171 patients in the *NPM1*^{mut} intermediate group would be considered as favorable according to the ELN2017 criteria, as well as 162 patients in the *NPM1*^{mut} adverse group were previously classified as intermediate risk. Therefore, our model was able to reclassify 33% of *NPM1*^{mut} AML patients in comparison to ELN2017 criteria.

Multivariate analysis of OS in *NPM1*^{mut} AML identified the following independent prognostic factors: *NPM1*^{mut} model (taking favorable group as reference, HR 1.6 for intermediate and HR 2.7 for adverse group, p<0.001); secondary or therapy-related AML (HR 1.8, p<0.001), WBC at diagnosis >100x10^3/µL (HR 1.5, p<0.001) and age >60 years (HR 1.4, p<0.001).

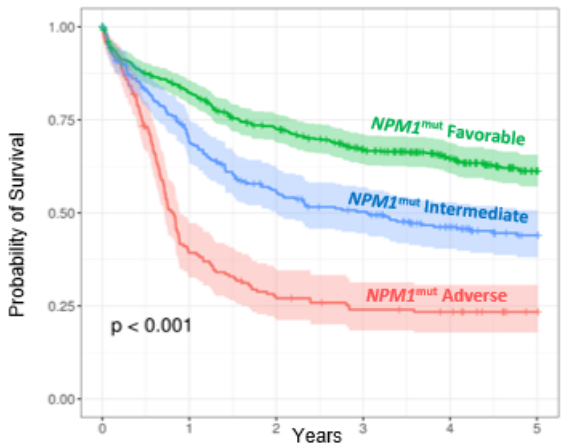
Image:

Figure 1. Classification criteria for *NPM1*^{mut} AML (A) and Kaplan-Meier OS analysis in each group (B)

A

Proposed risk group in *NPM1*^{mut} AML	Criteria
Adverse (18%)	• *FLT3*-ITD^{high} + *DNMT3A*^{mut} • *TP53*^{mut}
Intermediate (26%)	• *FLT3*-ITD^{high} + *DNMT3A*^{wt} • *FLT3*-ITD^{low} + *DNMT3A*^{mut} • Absence *FLT3*-ITD + *DNMT3A*^{mut} without any favorable (*PTPN11*^{wt}+*NRAS*^{wt}+*RAD21*^{wt}+*KRAS*^{wt})
Favorable (56%)	• Not meeting Adverse or Intermediate criteria

B



Summary/Conclusion:

Analysis of large *NPM1*^{mut} AML cohorts allows the discovery of co-mutation patterns associated with prognostic outcome. In accordance, we propose a new genetic stratification model for *NPM1*^{mut} AML that identifies 3 groups with different OS and RFS. This model improves ELN2017 criteria as it is able to correctly reclassify 33% of *NPM1*^{mut} AML patients.