

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

Queen's University Belfast - Research Portal:

Link to publication record in Queen's University Belfast Research Portal

Publisher rights

Copyright 2022 the authors.

This is an open access article published under a Creative Commons Attribution-NonCommercial-NoDerivs License (https://creativecommons.org/licenses/by-nc-nd/4.0/), which permits distribution and reproduction for non-commercial purposes, provided the author and source are cited.

General rights

Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.

Open Access

This research has been made openly available by Queen's academics and its Open Research team. We would love to hear how access to this research benefits you. – Share your feedback with us: http://go.qub.ac.uk/oa-feedback

HemaSphere



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

Topic: 04. Acute myeloid leukemia - Clinical

<u>Alberto Hernández-Sánchez^{1, 2},</u> Ángela Villaverde-Ramiro², Javier Martínez Elicegui², Teresa González^{2, 3}, Axel Benner⁴, Eric Sträng⁵, Gastone Castellani⁶, Caroline A. Heckman^{7, 8}, Jurjen Versluis⁹, María Abáigar^{2, 3}, Marta Sobas¹⁰, Raúl Azibeiro^{1, 2}, Laura Tur¹¹, Peter JM Valk⁹, Klaus H Metzeler¹², Rosa Ayala¹³, Daniele Dall'Olio⁶, Jesse Tettero¹⁴, Joaquín Martínez-López¹³, Hervé Dombret¹⁵, Marta Pratcorona¹⁶, Frederik Damm⁵, Ken I Mills¹⁷, Jiří Mayer¹⁸, Christian Thiede¹⁹, Maria Teresa Voso²⁰, Guillermo F Sanz^{21, 22}, Frederico Calado²³, Konstanze Döhner²⁴, Verena I Gaidzik²⁵, Michael Heuser²⁶, Torsten Haferlach²⁷, Amin T Turki^{28, 29}, Dirk Reinhardt²⁸, Rubén Villoria Medina¹¹, Michel van Speybroeck³⁰, Renate Schulze-Rath³¹, Martje Barbus³², John E Butler³³, Jesús M Hernández Rivas^{1, 2, 3}, Brian JP Huntly³⁴, Gert J Ossenkoppele^{14, 35, 36}, Hartmut Döhner²⁴, Lars Bullinger⁵

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 Broand 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 UIm, UIm, 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 Germang 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;³⁶ Cancer Ce

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.

Copyright Information: (Online) ISSN: 2572-9241

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.

Disclaimer: Articles published in the journal HemaSphere exclusively reflect the opinions of the authors. The authors are responsible for all content in their abstracts including accuracy of the facts, statements, citing resources, etc.

^{© 2022} the Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the European Hematology Association. This is an open access Abstract Book distributed under the Attribution-NonCommercial-NoDerivs (CC BY-NC-ND) which allows third parties to download the articles and share them with others as long as they credit the author and the Abstract Book, but they cannot change the content in any way or use them commercially.

HemaSphere



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 >100x10³/µL (HR 1.5, p<0.001) and age >60 years (HR 1.4, p<0.001).

Image:

Copyright Information: (Online) ISSN: 2572-9241

© 2022 the Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the European Hematology Association. This is an open access Abstract Book distributed under the Attribution-NonCommercial-NoDerivs (CC BY-NC-ND) which allows third parties to download the articles and share them with others as long as they credit the author and the Abstract Book, but they cannot change the content in any way or use them commercially.

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.

Disclaimer: Articles published in the journal HemaSphere exclusively reflect the opinions of the authors. The authors are responsible for all content in their abstracts including accuracy of the facts, statements, citing resources, etc.

HemaSphere



А Proposed risk group Criteria in NPM1^{mut} AML FLT3-ITD^{high} + DNMT3A^{mut} Adverse (18%)TP53^{mu} FLT3-ITD^{high} + DNMT3A^{wt} FLT3-ITD^{low} + DNMT3A^{mut} Intermediate Absence FLT3-ITD + DNMT3Amut without (26%)any favorable (PTPN11wt+NRASwt+RAD21wt+KRASwt) Favorable Not meeting Adverse or Intermediate (56%) criteria в 1.00 0.75 NPM1^{mut} Favorable Probability of Survival VPM1m ^{ut} Intermediate 0.50 NPM1^{mut} Adverse 0.25 p < 0.001 0.00 ż Years

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

Copyright Information: (Online) ISSN: 2572-9241

© 2022 the Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the European Hematology Association. This is an open access Abstract Book distributed under the Attribution-NonCommercial-NoDerivs (CC BY-NC-ND) which allows third parties to download the articles and share them with others as long as they credit the author and the Abstract Book, but they cannot change the content in any way or use them commercially.

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.

Disclaimer: Articles published in the journal HemaSphere exclusively reflect the opinions of the authors. The authors are responsible for all content in their abstracts including accuracy of the facts, statements, citing resources, etc.