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621.LYMPHOMAS: TRANSLATIONAL-MOLECULAR AND GENETIC

Optical Genome Mapping Provides New Molecular Insights in High-Risk Mantle Cell Lymphoma: A Lysa Study

Sophie Kaltenbach^{1,2}, Yannick LE Bris, PhD³, Bruno Tesson⁴, Aurore Touzart, MD PhD⁵, Guillaume Charbonnier⁶, Vincent Ribrag⁷, Remy Gressin, MD⁸, Clementine Sarkozy⁹, Catherine Thieblemont, MD PhD¹⁰, Franck Morschhauser, MDPHD¹¹, Corinne Haioun, MD PhD¹², Violaine Safar, MD¹³, Herve Ghesquieres, MD PhD¹⁴, Barbara Burroni, MD¹⁵, Marie-Helene Delfau, MDPHD¹⁶, Elizabeth A. Macintyre, MD PhD¹⁷, Mary Callanan¹⁸, Vahid Asnafi¹⁹, Steven Le Gouill, MD PhD²⁰, Olivier Hermine²¹, Morgane Cheminant²²

¹ Necker University Hospital, AP-HP, Paris, FRA

² Hematobiology, Necker University Hospital, Paris, France

³ Hematobiology, Nantes University Hospital, Nantes, France

⁴ Institut Carnot CALYM, Pierre Bénite, FRA

⁵ Institut Necker-Enfants Malades (INEM), Paris, FRA

⁶ Institut Necker, INEM, Paris, France

⁷ Institut Gustave Roussy, Villejuif, FRA

⁸ HOPITAL ALBERT MICHALLON, Department of Hematology, University Hospital Grenoble, Grenoble, France

⁹ Hematology departement, institut Curie, Paris, France

¹⁰ Assistance Publique-Hôpitaux de Paris, Hôpital Saint-Louis, Hemato-oncologie, Université de Paris, Paris, France

¹¹ CHRU de Lille, Hôpital Claude Huriez, Lille, FRA

¹² Lymphoid Malignancies Department, Henri Mondor University Hospital, AP-HP, Créteil, France

¹³ Hematology Department, Hôpital Lyon Sud - HCL, Lyon, France

¹⁴ Hematology Department, Hopital Lyon Sud - HCL, Lyon, France

¹⁵ Pathology, Cochin, Paris, FRA

¹⁶ Hemato-biology, Henri Mondor University Hospital, Créteil, France

¹⁷ Laboratory of Onco-Hematology, Necker Enfants-Malades Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Université Paris Cité, Paris, France, Paris, FRA

¹⁸ INSERM U823, Grenoble, FRA

¹⁹ Université Paris Descartes Sorbonne Cité, Institut Necker-Enfants, Paris, FRA

²⁰ Hematology Department, Institut Curie, Paris, France

²¹ Hematology Department, Necker University Hospital, Paris, France

²² Department of Hematology, Necker Hospital, APHP, Paris, France

Introduction

Around 5-10% of mantle cell lymphoma (MCL) patients are primary refractory to chemotherapy. They have an extremely dismal prognosis, as do responsive patients that relapsed within 12 months. Despite better understanding of risk factors and evolving classifications, these scores do not predict all high-risk patients and were not designed to guide treatment strategy in newly diagnosed MCL. Optical genome mapping (OGM) is a cutting-edge technology developed for genome-wide detection of structural variants (SVs) including balanced and unbalanced translocations, inversions, insertions, deletions, duplications as well as copy number variations (CNVs).

Methods

High-risk (HR) patients included in the prospective phase III LyMa trial (NCI NCT00921414; Le Gouill *et al.* NEJM 2017), were identified as patients experiencing early progression of disease (i.e. within 1 year after randomization). We performed OGM in the HR cohort using available frozen tumoral tissue. Low-risk patients (LR) were used as a control. The data were analyzed with the Bionano Solve software.

Results

Among 299 MCL patients included in the LyMa trial, 31 high-risk MCL patients were identified (10.4%). OGM was performed in 15 patients: 8 HR and 7 LR. OGM successfully detected the t(11;14) in all patients. We detected a median of 38 SVs (range,

16-129) and 12 CNVs (range, 1-119) per case, higher in HR patients than in LR patients (median 51 vs. 32, $p=0.07$ for SVs; and 14 vs. 5, $p=0.11$ for CNVs). Chromothripsis and chromoplexia occurred in both cohorts, but breakage-fusion-bridge (BFB) cycles was only observed in 2 HR MCL. HR MCL were characterized by frequent loss of 17p/ *TP53* (63% vs. 0%, $p=0.03$), and rare deletions of 11q22-q23/ *ATM* (13% vs. 57%, $p=0.12$). Three HR patients had no *TP53* deletions, two of whom presented a gain of *BCL2*. Gain of *UBR5*, that influence transcription and posttranscription processes, was found in 3/8 HR patients compared to 1/8 LR patients. *MTAP* deletion that has been recently described as biomarkers predicting refractory MCL was found in 5/8 HR MCL and is associated with *CDKN2A/2B* deletions, compared to 0/8 LR. *MTAP* deletion was associated with *TP53* deletions in two HR MCL, that is supposed to confer resistance to PRMT5 targeted therapy (Sloan SL et al. *Blood* 2023). Deletion of the chromatin modifier *MEF2B* occurred in 3/8 HR MCL and 1/8 LR MCL. Two patients had deletion of *SMARCA4* at diagnosis, that confers resistance to the BCL-2 inhibitor venetoclax (Agarwal et al. *Nature Med* 2018). Mutations in the NF- κ B alternative pathway, responsible for resistance to ibrutinib, are found in both LR and HR patients.

Conclusion

In this small cohort of MCL patients included in a trial, complex structural alterations were identified by OGM at the time of diagnosis. OGM is a very promising technology that demonstrated its potential in the cytogenetic prognostic staging of MCL.

Disclosures Sarkozy: *Incyte Bioscience:* Consultancy, Other: Travel, Accommodations, Expenses; *BMS:* Consultancy; *Janssen:* Consultancy; *GSK:* Consultancy; *AbbVie:* Honoraria; *Gilead:* Other: Congress fees; *Roche:* Other: Travel, Accommodations, Expenses, Research Funding; *Prelude Therapeutics:* Consultancy; *Beigene:* Consultancy; *Lilly:* Honoraria; *Gilead:* Other: Travel, Accommodations, Expenses; *Takeda:* Other: Travel, Accommodations, Expenses. **Thieblemont:** *Paris University, Assistance Publique, hopitaux de Paris (APHP):* Current Employment; *Bayer:* Honoraria; *Kyte, Gilead, Novartis, BMS, Abbvie, F. Hoffmann-La Roche Ltd, Amgen:* Honoraria; *Takeda:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Kite:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel Expenses; *Incyte:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Collectis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel Expenses; *Hospira:* Research Funding; *Amgen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel Expenses; *Gilead Sciences:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel Expenses; *Novartis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel Expenses; *Roche:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Travel Expenses, Research Funding; *AbbVie:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel Expenses; *BMS/Celgene:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Travel Expenses, Research Funding; *Janssen:* Honoraria, Other: Travel Expenses. **Morschhauser:** *F. Hoffmann-La Roche Ltd, AbbVie, BMS, Genmab, Gilead, Novartis:* Consultancy; *F. Hoffmann-La Roche Ltd, Gilead, AbbVie:* Membership on an entity's Board of Directors or advisory committees. **Safar:** *Janssen:* Honoraria. **Ghesquieres:** *Gilead, Roche:* Consultancy; *Gilead, Roche, Bristol Myers Squibb, AbbVie, Novartis:* Honoraria. **Cheminant:** *Amgen:* Honoraria; *Innate Pharma:* Research Funding; *AstraZeneca:* Other: Travel accommodations and Meeting inscription; *Abbvie:* Research Funding.

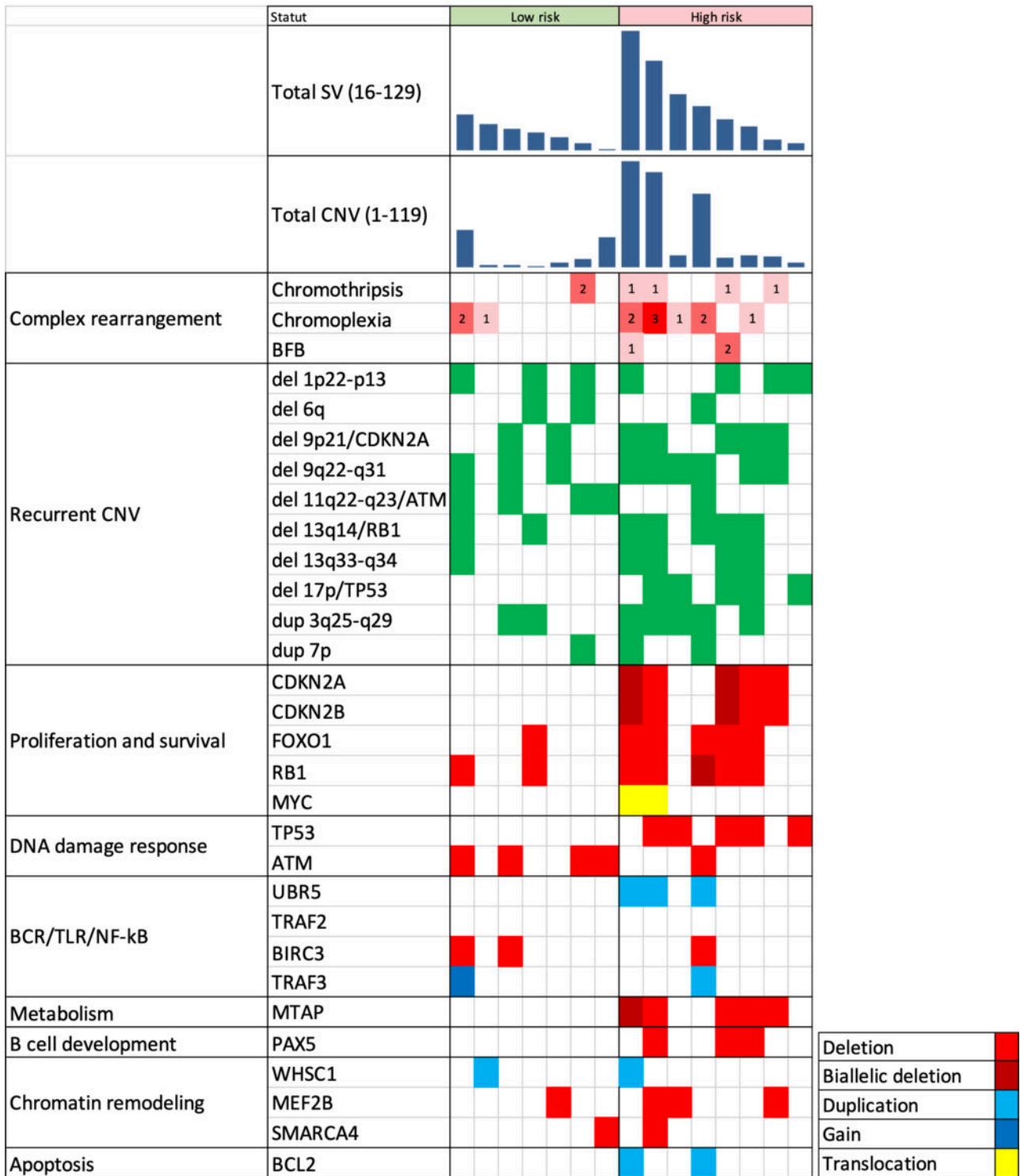


Figure 1

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