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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

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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-κB 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.

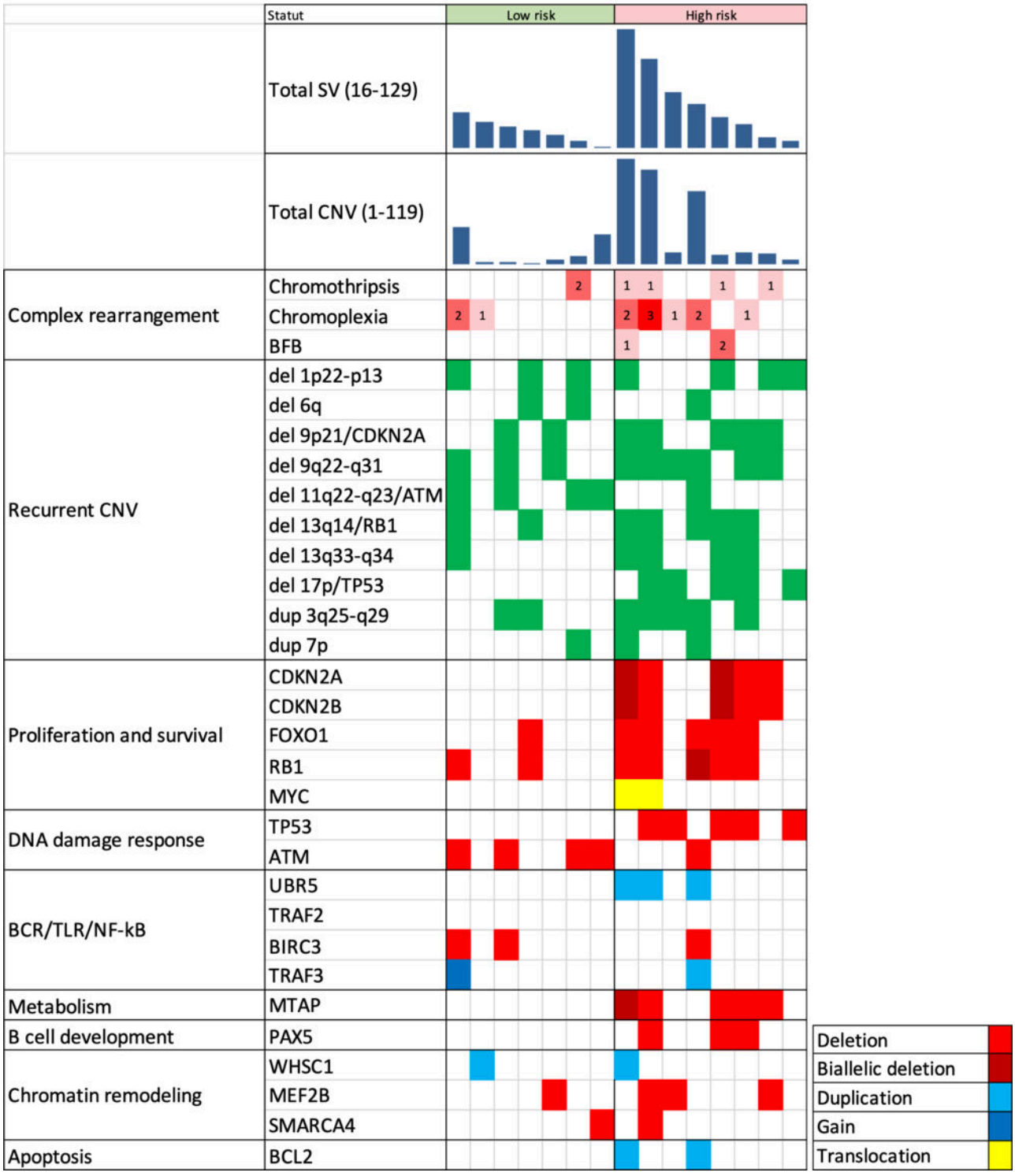

Figure 1

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