



The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

621.LYMPHOMAS: TRANSLATIONAL-MOLECULAR AND GENETIC

Genomic and Transcriptomic Profiles of Blastoid and Pleomorphic Mantle Cell Lymphoma Are Distinct from Classic Histology Mantle Cell Lymphoma

Preetesh Jain, MDMBBS,PhDDM¹, Holly A Hill, MS², Chi Young Ok, MD³, Alexander Nesmalov, PhD⁴, Vitaly Segodin⁵, Dmitry Tabakov, PhD⁶, Nikita Kotlov⁶, Pavel Zemskiy⁷, Eleonora Belykh⁸, Krystle Nomie, PhD⁶, Ahmed Fetooh, MD⁹, Rashmi Kanagal-Shamanna, MD¹⁰, Fatima Z Jelloul¹¹, Guilin Tang, MDPHD³, Francisco Vega, MDPHD¹², Nathan Fowler, MD⁶, Christopher R. Flowers, MD MS¹³, Michael L. Wang, MD¹⁴

¹ Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX

² Departments of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX

³ Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX

⁴ BostonGene Corporation, Waltham, MA

⁵ BostonGene Corporation, Boston

⁶ BostonGene, Corp., Waltham, MA

⁷ boston gene, MA, MA

⁸ Boston Gene corp, MA

⁹ Lymphoma/ Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX

¹⁰ Hematopathology, MD Anderson Cancer Center, Houston, TX

¹¹ Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX

¹² Department of Hematopathology, MD Anderson Cancer Center, Houston, TX

¹³ Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX

¹⁴ Lymphoma/ Myeloma, University of Texas MD Anderson Cancer Center, Houston, TX

Introduction - Patients (pts) with mantle cell lymphoma (MCL) with blastoid (B-MCL) and pleomorphic (P-MCL) histology are traditionally considered as high risk; however, there is a paucity of information regarding the differences between P-MCL and B-MCL compared to classic MCL (C-MCL) histology. In this study, we present a comprehensive genomic and transcriptomic portrait of B-MCL and P-MCL.

Methods - We conducted comprehensive molecular profiling using whole exome (WES) and bulk RNA sequencing (RNA seq) among the evaluable pt samples (n=260) from our center (MDA cohort) and previously reported cohorts from Bea et al (*PNAS* 2013) (n=29) and Agarwal et al (*Nature Medicine* 2019) (n=15) respectively. Pts with WES were (n=195) including n=151, n=29 and n=15 for MDA, Bea and Agarwal respectively while 175 pts underwent RNA sequencing (all MDA). This cohort study was conducted under an IRB approved protocol for MCL patients at our center. Patient characteristics, somatic mutation profiles, copy number abnormalities and gene expression profiles (GEP) were analysed. Lymph node, bone marrow, blood samples and any other tissue biopsies were utilized. DNA and RNA were extracted from FFPE sections from lymph nodes and non-nodal tissues. Joint WES and RNA-seq mutation calling, GEP, and transcriptomic cell deconvolution were performed using the BostonGene automated pipeline. WES and bulk RNA sequencing were performed with Illumina HiSeq4000 using a 76bp paired end configuration.

Results - Among the 195 pts with WES, the distribution of tissue types was 133 nodal, 33 bone marrow, 25 blood, 4 spleen and other tissues. Mutation distribution and copy number analysis was performed for 99 C-MCL, 72 B-MCL, and 20 P-MCL pts.

In the mutation profile, we found that the percentage of *ATM* mutations was comparable among the 3 pt groups (51%/50%/39%). The frequency of *TP53* mutations was significantly lower in C-MCL (23%) compared to B-MCL (51%) and P-MCL (39%) ($p < 0.001$; Figure 1). *NOTCH2* gain of function mutations were found in 11% of B-MCL and 4.6% of C-MCL but not detected in P-MCL. The *NFKB1E* Y254Sfs*13 mutation was exclusively found in B-MCL. Blastoid samples were enriched with *CCND1* E36K mutations (7 of 16 *CCND1* mut), while C-MCL had 2 of 16. P-MCL had a higher prevalence of *SMARCA4* and *DNMT3A* mutations compared to B-MCL and C-MCL.

We further observe that P-MCL pts exhibited higher polyploidy and aneuploidy than B-MCL and C-MCL ($p < 0.001$; Figure 2), indicating that compared to C-MCL, genomic instability decreased from P-MCL to B-MCL. The most frequent arm level amplifications in P-MCL compared to B-MCL were 8q (=MYC) (38%) and 18q (=BCL2) (38%). In C-MCL and B-MCL the 3q (=BCL6) was frequently amplified (28% and 30%). MALT1, Bcl2 and CARD11 gene amplifications were highest in P-MCL. These differences were further supported when the data were compared at the gene level. Comparison of the deletion frequencies revealed that 9p (CDKN2A/B) and 17p (TP53) were frequently lost in B and P-MCL (~40%). Del8p, 6q, 10q, and 16q were frequently deleted in P-MCL compared to B-MCL. At the segmental level, mostly altered segments included del9p21.1-24.3, del13q14.2-14.3, and del17p12-13.3 that span genes like *CDKN2A/B*, *miR15A*, and *TP53*.

Next, we performed GSEA analysis using RNA-seq data. The metabolic reprogramming pathway was upregulated in both B and P-MCL compared to C-MCL ($p = 0.0096$). The proportion of pts with an immune desert (D) "cold" tumor microenvironment associated with refractory disease was higher in P-MCL (50%) than in C or B-MCL.

Conclusions -B and P-MCL exhibit a distinct molecular profile compared to C-MCL. P and B-MCL have the highest degree of aneuploidy and exhibit an immune cold tumor microenvironment. Further studies are ongoing to refine the molecular differences among B and P-MCL compared to C-MCL.

Disclosures Jain: AstraZeneca: Consultancy, Honoraria. **Nesmalov:** BostonGene: Current Employment, Current equity holder in private company, Current holder of stock options in a privately-held company, Patents & Royalties: patents. **Tabakov:** BostonGene: Current Employment, Current equity holder in private company, Current holder of stock options in a privately-held company. **Kotlov:** BostonGene, Corp.: Current Employment, Current equity holder in private company, Current holder of stock options in a privately-held company, Patents & Royalties. **Nomie:** BostonGene, Corp.: Current Employment, Current equity holder in private company, Current holder of stock options in a privately-held company. **Vega:** Allogene: Research Funding; Geron: Research Funding. **Fowler:** Gilead: Consultancy, Research Funding; Roche: Consultancy, Research Funding; CelGene: Consultancy, Research Funding; BostonGene: Current Employment, Current equity holder in private company, Current holder of stock options in a privately-held company. **Flowers:** Takeda: Research Funding; Xencor: Research Funding; Pharmacyclics Jansen: Consultancy; Genmab: Consultancy; Karyopharm: Consultancy; N-Power Medicine: Consultancy, Current holder of stock options in a privately-held company; Amgen: Research Funding; Cellectis: Research Funding; Adaptimmune: Research Funding; Acerta: Research Funding; 4D: Research Funding; Spectrum: Consultancy; SeaGen: Consultancy; Abbvie: Consultancy, Research Funding; Nektar: Research Funding; Beigene: Consultancy; Bayer: Consultancy, Research Funding; Ziopharm: Research Funding; V Foundation: Research Funding; Guardant: Research Funding; Morphosys: Research Funding; Cancer Prevention and Research Institute of Texas: Research Funding; Burroughs Wellcome Fund: Research Funding; Allogene: Research Funding; National Cancer Institute: Research Funding; TG Therapeutics: Research Funding; Pharmacyclics: Research Funding; Genentech Roche: Consultancy, Research Funding; Novartis: Research Funding; Eastern Cooperative Oncology Group: Research Funding; Janssen Pharmaceuticals: Research Funding; Kite: Research Funding; Sanofi: Research Funding; Gilead: Consultancy, Research Funding; Pfizer: Research Funding; Iovance: Research Funding; Celgene: Consultancy, Research Funding; Foresight Diagnostics: Consultancy, Current holder of stock options in a privately-held company; Denovo Biopharma: Consultancy; CPRIT Scholar in Cancer Research: Research Funding. **Wang:** Scripps: Honoraria; Meeting Minds Experts: Honoraria; Juno Therapeutics: Research Funding; Genentech: Research Funding; Celgene: Other: Travel, Research Funding; WebMD: Honoraria; Studio ER Congress: Honoraria; MD Education: Honoraria; MJH Life Sciences: Honoraria; Moffit Cancer Center: Honoraria; NIH: Honoraria; Nurix: Honoraria; Medscape: Honoraria; Molecular Templates: Research Funding; Loxo Oncology: Research Funding; Eastern Virginia Medical School: Honoraria; Genmab: Honoraria, Research Funding; i3Health: Honoraria; IDEOlogy Health: Honoraria; Vincerx: Research Funding; VelosBio: Consultancy, Research Funding; Bantam Pharmaceutical: Honoraria; CAHON: Honoraria; Dava Oncology: Honoraria, Other: Travel; Oncology Specialty Group: Honoraria; Practice Point Communications (PPC): Honoraria; Onclive: Honoraria; Physicians Education Resources (PER): Honoraria, Other: Travel; BioInvent: Consultancy, Honoraria, Research Funding; Bristol Myers Squibb: Consultancy, Honoraria; Deciphera: Consultancy; DTRM Biopharma (Cayman) Limited: Consultancy; Genentech: Consultancy; InnoCare: Consultancy; Janssen: Consultancy, Honoraria, Research Funding; Kite Pharma: Consultancy, Honoraria, Other: Travel, Research Funding; Leukemia & Lymphoma Society: Consultancy, Honoraria; Eli Lilly and Company: Consultancy, Research Funding; Merck: Consultancy, Honoraria; Miltenyi Biomedicine: Consultancy; Milken Institute: Consultancy; Oncternal: Consultancy, Research Funding; Parexel: Consultancy; Pepromene Bio: Consultancy; Pharmacyclics: Consultancy, Honoraria, Research Funding; BeiGene: Consultancy, Honoraria, Research Funding; Be Biopharma: Consultancy; AstraZeneca: Consultancy, Honoraria, Other: Travel, Research Funding; Amphista Therapeutics Limited: Consultancy; ADC Therapeutics America: Consultancy; Acerta Pharma: Consultancy, Honoraria, Research Funding; AbbVie: Consultancy, Honoraria.

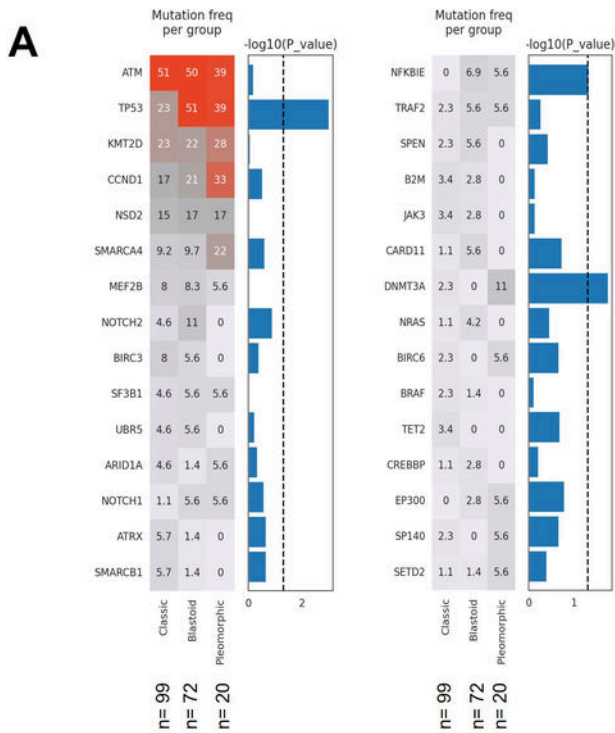


Figure 1. Frequency of mutations (% of samples related to each subtype) in different genes across classic MCL (C-MCL), blastoid MCL (B-MCL), and pleomorphic MCL (P-MCL).

Figure 1

<https://doi.org/10.1182/blood-2023-181319>

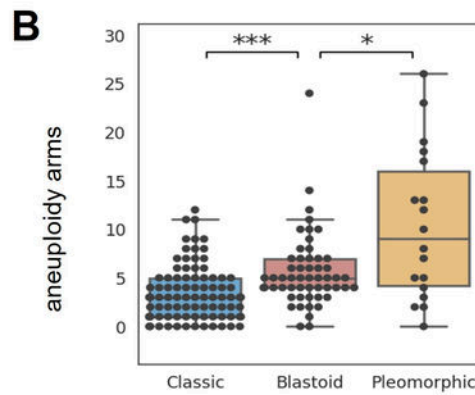


Figure 2. Number of aneuploidy chromosomal arms in classic MCL (C-MCL), blastoid MCL (B-MCL), and pleomorphic MCL (P-MCL). * p < 0.05; *** p < 0.001