Abstract #7 | Poster

Building a Genomic Meta-Cohort of 1,029 Primary CNS Lymphoma: Age-Associated Mutational Patterns from 27 Harmonized Cohorts

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OBJECTIVE: Primary Central Nervous System Lymphoma (PCNSL) is an aggressive lymphoma with a poor prognosis. Due to its low incidence, its molecular landscape remains incompletely defined, although an enrichment in the MCD/C5 molecular subcluster of diffuse large B-cell lymphoma (DLBCL) has been previously described. The aim of this study was to synthesize findings from genomic cohorts with limited sample sizes to identify recurrent somatic alterations and evaluate genetic signatures associated with clinical features such as age, progression-free survival (PFS), and overall survival (OS).

METHODS: This retrospective genomic analysis of PCNSL patients (n = 1,029) involved analysis of next-generation sequencing (NGS) data from of 27 independently published cohorts. Genomic annotation was harmonized across cohorts using post-processed mutation and copy number calls, and mutational co-occurrence was analyzed. The cohort includes profiles from whole exome/genome sequencing data (33.2%, n=342) as well as targeted panel data (66.8%, n=687).

RESULTS: We found that the genomic landscape of PCNSL is age-dependent, with elderly patients being more likely to harbor the MCD mutational signature. The five genes with the highest mutation frequency across the harmonized cohort were *MYD88* (62.9%), *PIM1* (51.0%), *CD79B* (43.8%), *BTG2* (34.6%), and *KMT2D* (30.1%). The median age at diagnosis was 65 years. We observed a significantly positive correlation between advancing age and mutations associated with the MCD subcluster and BCR/NF-κB signaling. The larger cohort size enables more stable estimation of driver mutation frequencies and enables detection of the ‘long tail’ of recurrent alterations in genes mutated in fewer than 5% of cases, which were underpowered in smaller existing studies.

CONCLUSIONS: We synthesized a large cohort by analyzing the somatic landscape of patients with PCNSL. We plan to make our cohort available to the scientific community as a interactive database resource. Preliminary findings from our analysis will be presented at the meeting. Future analyses will include: (1) unsupervised clustering (e.g. NMF) to define molecular subtypes beyond the MCD classification; (2) correlation of genomic signatures with PFS and OS; (3) clonal evaluation in PCNSL at the cohort level using cancer cell fraction (CCF).