Clinical Correlation of Immune-Molecular Profiles in Primary Central Nervous System Lymphoma

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Conflicts of interest

JKD: advisory board of Eli Lilly/Loxo.
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MWMP: Takeda: Consulting or Advisory Role.
JSPV: Secura Bio: Consulting or Advisory Role.
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Introduction
Primary central nervous system lymphoma (PCNSL) is a rare and aggressive lymphoma. Despite intensive polychemotherapy 60% of PCNSL patients experience chemorefractory or relapsed disease with limited second line treatment options resulting in a poor prognosis. New immune-modulating precision medicines are successfully emerging in other lymphomas, however the effective use of these therapies in PCNSL is still hampered by a lack of understanding of the immune-molecular background of PCNSL in correlation with clinical outcome. The aim of this large immune-molecular PCNSL study was to correlate detailed molecular data with clinical outcomes.

Methods
A large and homogenous cohort of PCNSL patients diagnosed between 2008 and 2023 from 12 Dutch and Belgian hospitals of whom diagnostic FFPE material was available were included. Only patients treated with ≥1 cycle of HD-MTX ≥3g/m2 per cycle with curative intent, with and without consecutive consolidation therapy were included. In-depth molecular DNA analysis was performed by targeted next-generation sequencing (tNGS) using an in-house designed and validated BLYMFv2 panel, including 128 B-cell lymphoma-relevant genes. Targeted gene-expression profiling (GEP) was performed using the NanoString nCounter technology with the BLYMF777 panel. This panel comprises probes for 777 genes pivotal in assessing the activity of multiple pathways, including NFκB, JAK/STAT, MAPK, NOTCH, and PI3K pathways, as well as consensus clustering, LAMIS signature, and Ecotyper classification and will be used to evaluate essential pathways and identify key interactions in the tumor microenvironment.

Results
Molecular DNA analysis was successful in 156 patients. A high proportion of NF-kB (associated) genes were found to be mutated in this cohort, *MYD88* (69%), *PIM1* (59%), *CD79B* (43%), *BTG2* (33%), and *TBL1XR1* (33%). All PCNSL patients showed at least one mutation or copy number alteration using the BLYMFv2 NGS panel and the median mutational load in PCNSL was 12 mutations (range 1 – 42). Frequent simultaneous mutations in *MYD88* and *CD79B* were observed. There were no clear differences found between the chemorefractory group and the group of patients that primarily showed response to treatment.

GEP data was collected for 218 patients and revealed three distinguishable groups. Further specific GEP analyses on functional pathway activity and the tumor microenvironment are still ongoing and the results will be presented at the DHC congress.

Conclusion
This multicenter study evaluates the immune-molecular profiles of a large PCNSL cohort in correlation with clinical response. *MYD88*, *PIM1*, *CD79B*, *BTG2*, and *TBL1XR1* were frequently mutated in this cohort without significant differences between the chemorefractory and primary response group. The immune-molecular analysis of this study could provide background for optimization of PCNSL treatment with targeted therapies which potentially improves the inferior prognosis of PCNSL patients.