THE TUMOUR MICROENVIRONMENT AND GENETIC PROFILE OF EBV+ PRIMARY CNS LYMPHOMAS IN AMENABLE TO COMBINATION 3RD PARTY EBV-SPECIFIC VST, IBRUTINIB AND TRITUXIMAB.

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INTRODUCTION: Primary CNS Lymphomas (PCNSL) with diffuse large B-cell lymphoma histology in the immunosuppressed, e.g. HIV+ PCNSL (i.e. AIDS-related PCNSL) or organ-transplants (EBV+ PCNSL-PTLD), have dismal outcome (median survival 8 months) and are characterized by EBV positivity. However, incidence is low, biopsy material limited and characterization minimal. Patients are typically excluded from clinical trials.

METHODS: We used targeted sequencing and digital multiplex gene expression to compare the genetic landscape and tumor microenvironment (TME) of 91 PCNSL tissues all with diffuse large B-cell lymphoma histology. Forty-seven were EBV tissue-negative: 45 EBV- HIV- PCNSL and 2 EBV- HIV+ PCNSL; and 44 were EBV tissue-positive: 23 EBV+ HIV+ PCNSL and 21 EBV+ HIV- PCNSL. Findings led to successful off-label treatment of 2 patients, and subsequent implementation of a rationally designed combination therapy of a blood brain barrier crossing small drug inhibitor, 3rd party EBV-specific VST therapy and anti-CD20 monoclonal antibody.

RESULTS: As expected, EBV- HIV- PCNSL had frequent MYD88, CD79B, and PIM1 mutations, and enrichment for the activated B-cell (ABC) cell-of-origin subtype. In contrast, these mutations were absent in all EBV tissue-positive cases and ABC frequency was low. Mutational burden was much lower in EBV+ PCNSL than EBV- PCNSL. Mutations that mediate resistance to BTK inhibitors were absent. Furthermore, copy number loss in HLA class I/II and antigen-presenting/processing genes were rarely observed, indicating retained antigen presentation. To counter this, EBV+ HIV- PCNSL had a tolerogenic TME with elevated macrophage (CD68, CD163) and immune-checkpoint (PD-L1, PD-L2, LAG3, TIM-3) gene expression, whereas AIDS-related PCNSL had low CD4 gene counts. Two organ-transplant patients with EBV+ PCNSL were treated with the BTK inhibitor ibrutinib, 3rd party EBV-specific VST (generated using the Miltenyi platform) and rituximab. PK confirmed therapeutic CSF levels, including a patient on haemodialysis. EBV-specific VST did not engraft. Toxicity was manageable and both patients are in long-term remission. Based on these findings, a phase I Australian-wide investigator-led study of 20 patients was conducted through the Australian Leukaemia Lymphoma Group. Accrual was completed a year early, despite COVID. Updated clinical results to most recent follow-up will be presented.

CONCLUSION: EBV-associated PCNSL in the immunosuppressed is immunobiologically distinct from EBV- HIV- PCNSL, and, despite expressing an immunogenic virus, retains the ability to present EBV antigens. Results provide a framework for targeted treatment.