P1250 EU-SOX11CCND1: A NOVEL IMMUNOCOMPETENT MURINE MODEL OF MANTLE CELL LYMPHOMA

Topic: 20. Lymphoma Biology & Translational Research

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Background:

Mantle cell lymphoma (MCL) is an incurable B cell malignancy, comprising 5% of non-Hodgkin lymphomas (NHL) diagnosed annually and associated with a poor prognosis due to emergence of resistance to immuno-chemotherapy and targeted agents. The average overall survival of patients with MCL is 4-6 years and for most patients who progress on targeted agents, survival remains at a dismal 3-8 months. There is a major unmet need to identify new therapeutic approaches that are well tolerated to improve treatment outcomes and quality of life.

Immunotherapy has shown great promise in MCL, with the recent FDA approval of Brexucabtagene autoleucel for R/R MCL. In order to optimize the preclinical testing of immunotherapy for MCL, immunocompetent mouse models are essential; there are currently fewer than five available making new models very valuable for MCL researchers.

Aims:

The C57BL/6J-Tg(Eµ-sox11-GFP, Eµ-ccnd1) or Eµ-SOX11CCND1 transgenic mouse model utilizes two key genes in MCL. SOX11 has been shown to be a driver of MCL, with overexpression in 80-90% of cases, and is highly correlated with more aggressive disease. CCND1 overexpression is a hallmark of MCL, where the gene translocation to the IgH promotor is frequently used to diagnose MCL from other NHLs. We show this model recapitulates an MCL-like tumor burden, displays an altered immune environment, and test the effects of the selective PRMT5 inhibitor PRT382.

Methods:

This model spontaneously develops CD19+/CD5+/CD23- lymphoma which progresses with splenomegaly, cytopenias, lymphadenopathy, and pre-mature death. Lymphoma cells from a founder were passaged through additional wild type, immune competent C57bl/6j mice through adoptive transfer and 100% of engrafted animals developed MCL-like tumor burden. This model can be utilized as a systemic model of MCL via intravenous (iv) tail vein or subcutaneous (sc) flank engraftment and reach early removal criteria by approximately day 21 showing disease pathology consistent with MCL. We created a luciferase positive clone that allows us to detect tumor burden by IVIS as early as one week post engraftment and to track disease progression. PRT382 was dosed orally and spectral flow was used to comprehensively monitor the immune response.

Results:

PRT382, in this model of MCL provided a significant survival advantage (18 vs 67 days, p<0.0001) as well as a reduction in disease burden as determined by flow cytometry. This data supports the results we have seen with PRMT5 inhibition in pre-clinical models of human MCL and reinforce the MCL disease characteristics of this model.

Comprehensive immune monitoring was performed on control and diseased mice. Analysis blood, spleen, bone marrow, and tumor showed distinct immune signatures within each compartment. We observed significant shifts in the ratio of Ly-6C+/Ly-6G- and Ly-6C(low/-)/Ly-6G+ myeloid cells, enrichment of CD8+ T cells, and depletion of...
mature B cells in the spleen. Markers of immune exhaustion including PD1 and PDL1 were increased on T cells, CD11b+, and lymphoma cells in MCL burdened mice. These expression patterns have also been described in human samples, validating the immune landscape of this model. PRMT5 inhibition alters several of these population, details of which will be shared.

**Summary/Conclusion:**

These results support the Eµ-SOX11CCND1 as an attractive model to understand the pathology of MCL and how disease burden and treatment influences host adaptive and innate immune networks. We will use this model to explore mechanisms of resistance to immunotherapy and create new treatment strategies for MCL.