Identifying patients with asymptomatic Waldenstrom's Macroglobulinemia (AWM) who are at the highest risk of progression may help determine when to treat to prevent the development of disease. Current risk stratification systems rely on clinical variables only, but tumor-intrinsic and immune factors could inform patient prognostication and therapy selection. We performed single-cell RNA-sequencing on bone marrow (BM) tumor and immune cells from 30 patients with AWM/WM. Despite their early stage, patients with AWM presented extensive immune dysregulation, with certain alterations present even in patients with no discernible evidence of BM infiltration by WM cells. Patients with AWM showed disease-specific depletion of interferon (IFN)-stimulated T & NK cells, despite normal levels of IFN in their circulation. Hypo-responsiveness to IFN and NK cell functionality improved with exogenous administration of IFN. A *DUSP22*/*CD9*-positive subtype of WM was identified, which was associated with lymph node-tropism and *CXCR4*-WT status. Lastly, a progression signature, marked by *CXCR4* levels but independent of *CXCR4* mutation status, appeared to increase in activity between patients with IgM MGUS and WM and was associated with increasing BM burden in patients with WM. Incorporating variables related to tumor and immune biology in risk stratification models can help advance WM research and clinical practice.