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ORAL ABSTRACTS

605.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: LYMPHOID NEOPLASMS

Qpctl Inhibition, By Targeting the Inflammatory Tumor Microenvironment, Constitutes a Novel Therapeutic Approach for Diffuse Large B-Cell Lymphoma

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We have previously described that diffuse large B-cell lymphomas (DLBCL) harboring an inflammatory and immunosuppressive microenvironment (i.e., IN-LME) carry independent poor prognosis while proof-of-principle experiments modifying the composition of the LME were sufficient to induce lymphoma regression in mice models (*Kotlov, Cancer Discovery 2021*). However, identification of pharmaceutical approaches that by modifying the LME will induce an anti-lymphoma effect while being suitable for short-term human translation remains challenging. The IN-LME is characterized by the presence of pro-inflammatory and immunosuppressive chemokines and cytokines that frequently undergo post-translational modifications. QPCTL (glutaminyl-peptide cyclotransferase-like) is an intracellular enzyme that mediates a N-terminal pyroglutamylation of CD47 and several chemokines, including CCL2 and CCL7, ultimately resulting in their sustained expression and/or secretion. SC-2882 is a first-in-class specific QPCTL inhibitor that induces secondary proteolytic degradation of the monocyte chemoattractants CCL2 and CCL7 (*da Silva, Nature Immunology 2022)* and inactivation of the "do-not-eat-me" signal CD47 (*Logtenberg Nature Medicine 2019*).

In a dataset of 470 DLBCL patients we found that the expression of QPCTL correlates negatively with overall survival and progression free survival (0.019 and <0.001, respectively). To determine whether QPCTL could be a potential target in DLBCL, we investigated its expression along with its targets CCL2, CCL7 and CD47 in additional 216 DLBCL cases categorized by LME. We found that while QPCTL and CD47 are expressed at similar levels in all DLBCL cases regardless their COO class and LME category, CCL2 was highly expressed in DLBCL harboring a IN-LME ($p < 0.05$ vs. other LME categories), that also correlate with higher presence of tumor-associated macrophages (TAMs) and exhausted CD8+PD1 ^{HIGH} T cells ($p < 0.01$ and $p < 0.001$, vs. other LME categories, respectively). CCL7 was not expressed at detectable levels in majority of LMEs in DLBCL. In preclinical models, murine and human DLBCL cell lines expressed baseline QPCTL and CD47 while CCL2 and CCL7 expression (qPCR) and secretion (ELISA) increased at higher levels upon culturing these cells for 24 h embedded in splenic extracellular matrix 3D cultures.

Exposure of a panel of 3 murine and 5 human DLBCL cells to increasing concentrations of SC-2882 (vs. vehicle) for up to 72 h and up to a 10 micromolar dose had no noticeable decrease in cell viability or proliferation. However, SC-2882 (vs. vehicle) at nanomolar concentrations increased anti-Cd20-dependent lymphoma cell phagocytosis by *in vitro* differentiated macrophages (from splenic monocytes in mice and THP1 cells in humans) in 3D co-cultures ($p < 0.05$, for all conditions). To further test the anti-lymphoma effect of SC-2882 we used a murine GCB-DLBCL model by implanting GEMM-derived aggressive Ezh2 mutant (EZH2 ^{Y646}equivalent) + BCL2 amplified lymphoma cells in the spleen of immunocompetent C57BL/mice (n=14). After implantation, mice were randomized to receive SC-2882 by oral gavage (n=7) or vehicle (n=14) for 14 days. Tumor burden was followed by luciferase imaging (Caliper), and spleens were analyzed at sacrifice by multiparametric imaging, flow-cytometry, and spatial transcriptomics. Oral SC-2882 (vs. vehicle) induced a significant decrease in tumor growth ($p=0.0079$, Figure 1) without evidence of systemic toxicity by body weight, blood cell count and chemistry panel. Analysis of the LME in remnant splenic tumors showed in SC-2882 (vs. vehicle) treated mice a significant decrease in lymphoma cells and Ki67+ cells ($p<0.001$) as well as F480+ TAMs ($p<0.01$) while there was an increase of CD3+ T cell infiltration ($p<0.001$). We also

found a decrease in Cd4+Foxp3+ Tregs and increase in Cd8+Gzb+ cells in SC-2882 treated mice by flow-cytometry. These changes mirrored the findings in the spatial transcriptomics. Additional analysis of LME cell subpopulations by SC-RNA-seq is ongoing. Overall, these data indicate that QPCTL is a potential target in DLBCL, and that QPCTL inhibition exhibits potent anti-lymphoma effects primarily by targeting the IN-LME.

Disclosures Mullender: *Scenic Biotech:* Current Employment, Current holder of *stock options* in a privately-held company. **Scheepstra:** *Scenic Biotech:* Current Employment, Current holder of *stock options* in a privately-held company. **Evers:** *Scenic Biotech:* Current Employment, Current holder of *stock options* in a privately-held company. **Wuerthner:** *Scenic Biotech:* Current Employment, Current holder of *stock options* in a privately-held company.

Figure 1

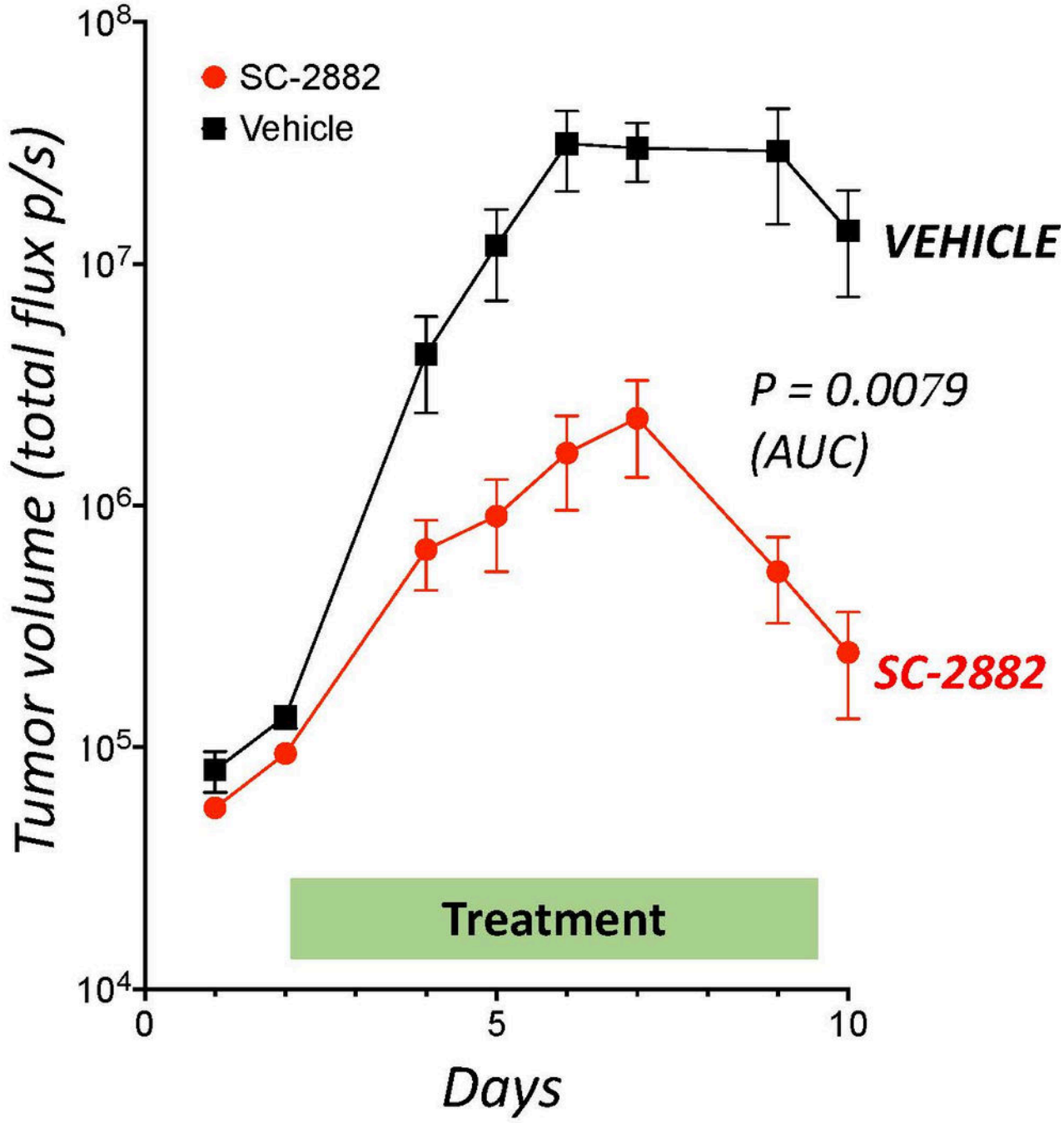

Figure 1

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