Title: (14 words/limit of 15 words)

Briquilimab Potently Blocks Stem Cell Factor (SCF)/c-Kit Signaling in Primary Human Mast Cells

Authors: (7 authors/limit of 8 authors)

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Body (248words/250 words limit)

Introduction: MC activation and survival relies on SCF/c-Kit signaling. Briquilimab is an aglycosylated monoclonal antibody (mAb) and potent blocker of SCF binding to c-Kit, leading to inhibition of SCF/c-Kit signaling and MC apoptosis. We evaluated briquilimab's inhibition of c-Kit phosphorylation and MC survival in comparison to a tool compound mAb that reduces c-Kit dimerization (JSP084) and the small molecule multi-tyrosine kinase inhibitor, imatinib.

Methods: Antibody binding to c-Kit, blockade of SCF ligand binding, c-Kit signaling, cell proliferation and survival were evaluated using M-07e, Ba/F3, and primary human MCs ($CD34^-$ $Fc\varepsilon RI^+c\text{-}Kit^+$) differentiated from mobilized peripheral $CD34^+$ cells.

Results: Briquilimab bound to c-Kit with relatively higher affinity than JSP084 in both MCs and M-07e cells. In M-07e cells, SCF ligand binding to c-Kit is almost completely blocked by briquilimab compared to partial blockade by JSP084. Both antibodies show similar inhibitory effects in MCs. Briquilimab was more potent than JSP084 at inhibiting c-Kit receptor internalization and c-Kit phosphorylation in both M-07e and MCs as well as SCF-mediated M-07e cell proliferation and SCF-dependent MC survival. Both briquilimab and JSP084 were significantly more potent than imatinib on inhibiting SCF/c-Kit signaling. Notably, at low concentrations, JSP084, but not briquilimab, appeared to be agonistic for c-Kit signaling, as shown by increased phosphorylation of c-Kit in M-07e cells and Akt, a downstream kinase of SCF/c-Kit anti-apoptotic signaling, in a Ba/F3 cell line stably expressing human c-Kit.

Conclusion: Briquilimab potently inhibits SCF/c-Kit signaling, via direct blockade of SCF, in cell lines and human MCs without exhibiting agonistic activity.