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

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INTRODUCTION

- Mast cell (MC) activation and survival relies on SCF/c-Kit signaling
- Briquilimab is an aglycosylated monoclonal antibody (mAb) and potently blocks 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

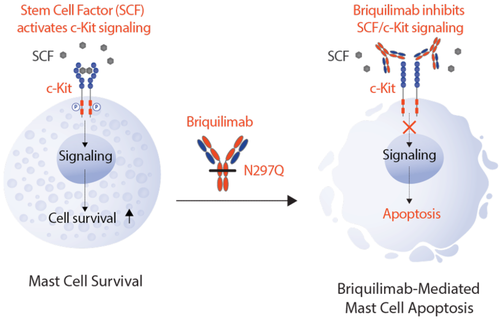

Figure 1. SCF/c-Kit signaling is essential for mast cell activation and survival. Briquilimab blocks SCF ligand-binding to c-Kit, inhibits SCF/c-Kit signaling, and induces MC apoptosis.

METHODS

- Antibody binding to c-Kit, blockade of SCF ligand binding, c-Kit phosphorylation, c-Kit receptor internalization, and 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

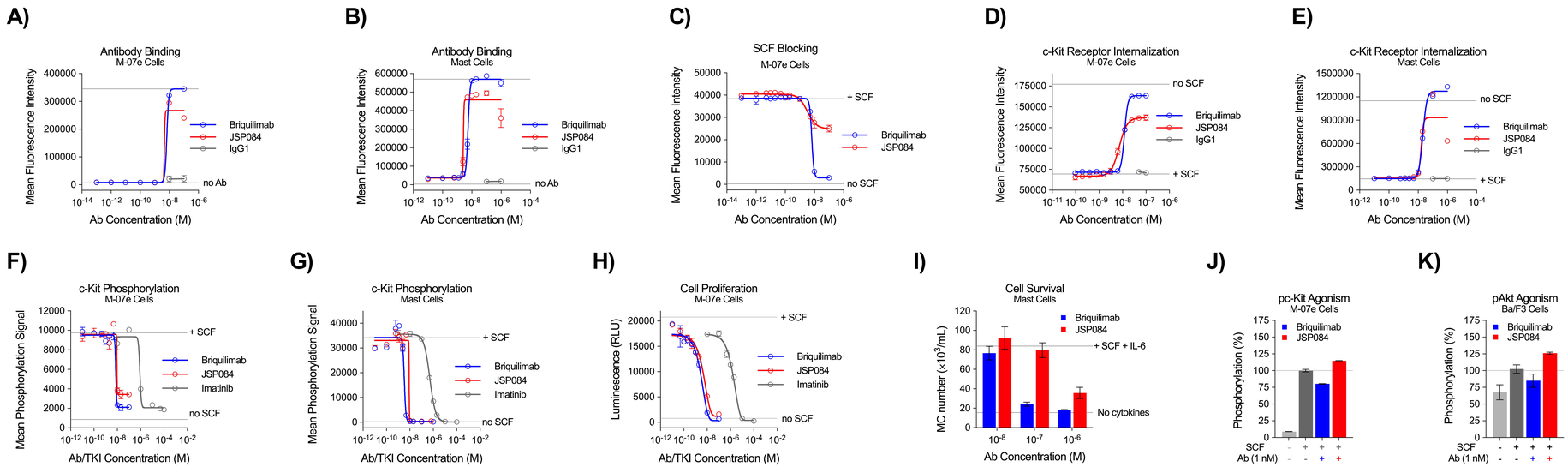

Figure 2. Briquilimab potently blocks SCF ligand binding and inhibits SCF/c-Kit signaling.
Briquilimab bound to c-Kit with relatively higher affinity than JSP084 in both (A) M-07e cells and (B) MCs. (C) SCF ligand binding to c-Kit was almost completely blocked by briquilimab compared to partial blockade by JSP084 in M-07e cells. Briquilimab was more potent than JSP084 at inhibiting (D,E) c-Kit receptor internalization, (F,G) c-Kit phosphorylation, (H) SCF-mediated M-07e cell proliferation and (I and ePoster R058) MC survival. Both briquilimab and JSP084 were significantly more potent than imatinib at inhibiting SCF/c-Kit signaling. JSP084 at low concentrations, but not briquilimab, increased phosphorylation of (J) c-Kit in M-07e cells and (K) 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
- Briquilimab appears to be more potent than JSP084, which blocks c-Kit dimerization. Additionally, in contrast to briquilimab, JSP084 exhibits potential agonistic c-Kit signaling activity at low concentrations
- Jasper is actively enrolling participants in a phase 1b/2a trial evaluating briquilimab in patients with chronic spontaneous urticaria (BEACON trial, NCT06162728) and in patients with chronic inducible urticaria (SPOTLIGHT trial, NCT06353971) and will commence enrolling participants for the proof-of-concept Phase 1b/2a asthma challenge study evaluating briquilimab in asthma