BSI-060T, a High Affinity, Fully Human Anti-Siglec-15 Antibody as an Alternative Immune Checkpoint Blocker

Zeyu Peng1, Xiaodong F. Liu2, Shukai Xia2, Jinyu Liu3, Hongyan Li3, Yuxiang Liu4, Hugh M. Davis4, Mingjui Chen2, Mark Z. Ma2

1Biosion, Inc., Nanjing, Jiangsu, China 2Biosion USA, Inc., Newark, DE, USA

Abstract

Background: Siglec-15 is a single-pass type I membrane protein that plays an important role in the immune-suppressive tumor microenvironment (TME). Siglec-15 has low expression levels in most normal human tissues but is highly expressed in a subset of myeloid cells of the TME and over-expressed in some solid tumors. Siglec-15 on tumor associated macrophages and tumor cells inhibits T cell proliferation and pro-inflammatory cytokine release. Therefore, targeting Siglec-15 may overcome a suppressive TME and enhance the anti-tumor activity of other immune checkpoint inhibitors.

Experimental procedures: Humanized mice were immunized with recombinant Siglec-15-ECD-Fc. The Biosion proprietary H+ (High-throughput, High-content and High-efficiency) antibody screening platform was used to identify a lead anti-Siglec-15 mAb candidate BSI-060T. Siglec-15 expression in different cancer types was assessed by immunohistochemistry (IHC) in conjunction with PD-L1. The ex vivo reverse of T cell suppression was determined by stimulating human peripheral blood mononuclear cells (PBMCs) with a suboptimal dose of immobilized OKT3 in the presence of recombinant human Siglec-15-Fc with and without BSI-060T. A pharmacokinetic study was carried out in cynomolgus monkeys to determine the exposure of BSI-060T over time. Tumor inhibitory activity of BSI-060T was evaluated in Siglec-15 humanized mice that were inoculated with MC38 cells overexpressing human Siglec-15.

Results: BSI-060T is a fully human IgG1x monoclonal antibody that binds to Siglec-15 protein with high affinity and blocks the interaction between Siglec-15 and its putative receptor LRRRC4C. BSI-060T shows cross-reactivity to monkey and mouse Siglec-15. In ex vivo T cell response assays, BSI-060T exhibits strong activity on reversing Siglec-15-mediated inhibition of CD8+ and CD4+ T cell proliferation and interferon-γ release. In a humanized Siglec-15 mouse syngeneic tumor model, BSI-060T induces significant inhibition of tumor growth. BSI-060T exhibits a favorable PK profile and dose-dependent exposure in monkey.

Conclusion: BSI-060T exhibits best-in-class biophysical properties and functional activities, supporting the initiation of clinical development in solid tumors.

BSI-060T Shows Higher Binding Affinity to Siglec-15 Than NC318 Analog

BSI-060T Binds to Cell Surface Siglec-15

BSI-060T Reverses Siglec-15-Mediated Inhibition of IFNγ Secretion from PBMCs Significantly Better Than NC318 Analog

BSI-060T Exhibits Anti-Tumor Activity in vivo

BSI-060T Exhibits a Favorable Pharmacokinetic Profile in Cynomolgus Monkeys

Summary

- BSI-060T is a fully human anti-Siglec-15 therapeutic antibody, exhibiting higher affinity and higher ex vivo bioactivity;
- BSI-060T induces significant inhibition of tumor growth in vivo with a favorable PK profile in cynomolgus monkeys;
- BSI-060T is an IND-ready asset with an IND submission and phase 1 initiation planned for 2022.