BSI-508, a Novel Bispecific Fusion Molecule Targeting PD1 and CD47 for Cancer Immunotherapy

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Abstract

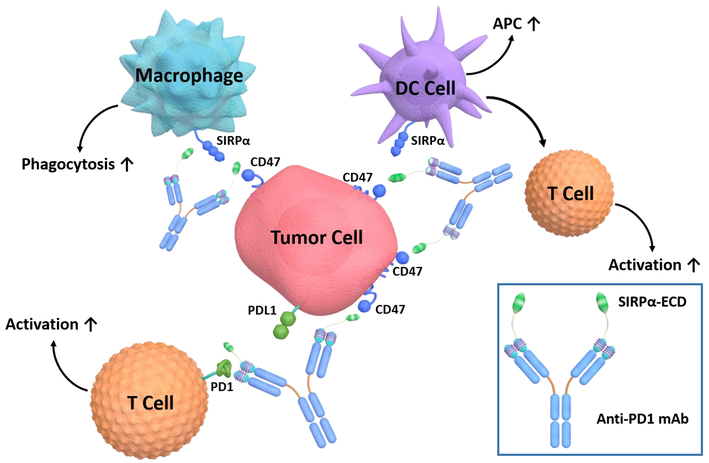
Introduction: While anti-PD1/PDL1 mAbs have shown success in the market only a small fraction of patients actually benefit from the therapies. Novel approaches to improve outcomes for patients who are resistant or refractory to current checkpoint inhibitors (CPIs) are needed. CD47 expressed on tumor cells can provide a "don't eat me" signal to antigen-presenting cells (APCs) via the binding to SIRPα. Blocking this interaction, enhancing the phagocytosis of tumor cells, has emerged as an effective alternative to current CPIs. Here we report on the generation and characterization of a novel bispecific fusion molecule BSI-508, composed of an anti-PD1 antibody fused with a SIRPα extracellular domain (ECD). The SIRPα-ECD binds CD47 and blocks the CD47/SIRPα-mediated cell signaling pathway. BSI-508 is designed to target PD1 on T cells and CD47 on tumor cells, providing tumor killing by T cells and macrophages synergistically.

Methods: An anti-PD1 mAb was identified from PD1 KO mice immunized with PD1-ECD-Fc and screened by our proprietary H^3 (High-throughput, High-content and High-efficiency) platform. Human SIRPα-V2-ECD1 was fused to the N-terminus of the heavy chain of the anti-PD1 antibody via a flexible linker. The binding activities and affinities to PD1 and CD47 were evaluated by ELISA, FACS and SPR. Ligand blocking activity was measured by ELISA and FACS. A cell-based reporter assay was used to evaluate the function of the anti-PD1 portion and a macrophage mediated phagocytosis assay was used to evaluate the function of the SIRPα-V2-ECD1 portion of the bispecific. B-hPD1/hPDL1/hSIRPα /hCD47 mice bearing B-hPDL1/hCD47 MC38 tumors were used to evaluate the tumor inhibitory activity of the bispecific fusion molecule.

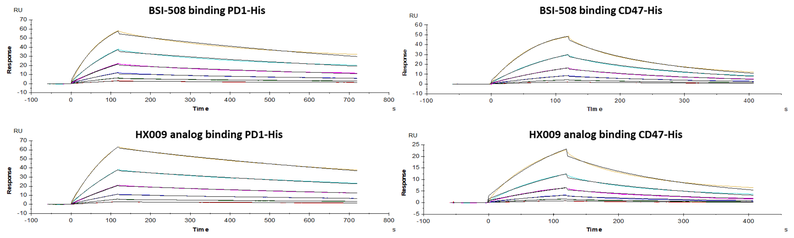
Results: BSI-508 demonstrated comparable activity to the parental anti-PD1 monoclonal antibody regarding PD1 binding and PD1/PDL1 blocking. It also exhibited comparable activity to the SIRPα-V2-ECD1-Fc fusion protein in CD47 binding and CD47/SIRPα blocking. BSI-508 was able to reverse PD1 mediated T-cell suppression and exhibited comparable bioactivity to the parental anti-PD1 antibody. The bispecific molecule showed comparable bioactivity to the SIRPα-V2-ECD1-Fc fusion protein in inducing macrophage mediated phagocytosis of Jurkat cells. In addition, BSI-508 showed superior antitumor efficacy *in vivo*.

Summary: BSI-508 is a novel anti-PD1 x anti-CD47 bispecific fusion molecule combining both T-cell activation and macrophage mediated phagocytosis together for superior tumor killing. BSI-508 demonstrates favorable biophysical and functional characteristics, supporting the initiation of development activities including manufacturing and IND-enabling studies.

MOA of BSI-508: Targeting PD1 and CD47

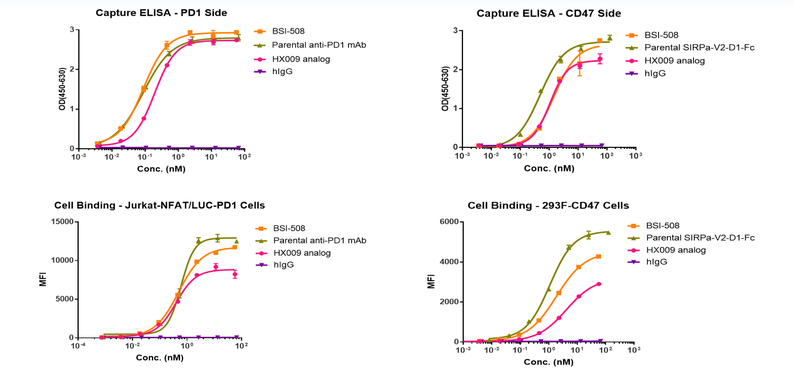


Binding Affinities of BSI-508 to PD1 and CD47

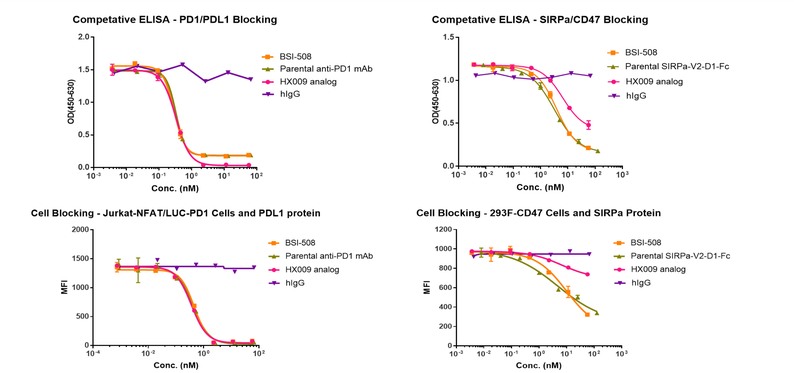


Antibody	Human PD1			Human CD47		
	K_a (1/Ms)	K_d (1/s)	K_D (M)	K_a (1/Ms)	K_d (1/s)	K_D (M)
BSI-508	2.61E+05	1.01E-03	**3.88E-09**	9.76E+05	1.39E-02	**1.43E-08**
HX009 analog	2.30E+05	9.71E-04	**4.23E-09**	4.98E+05	1.81E-02	**3.63E-08**

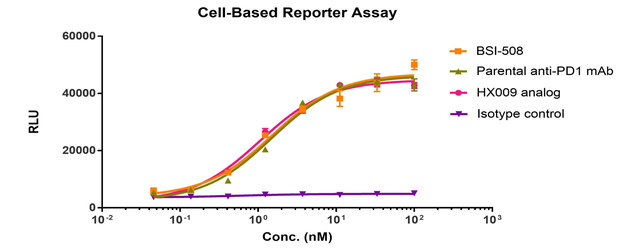
Binding Activities of BSI-508 to PD1 and CD47



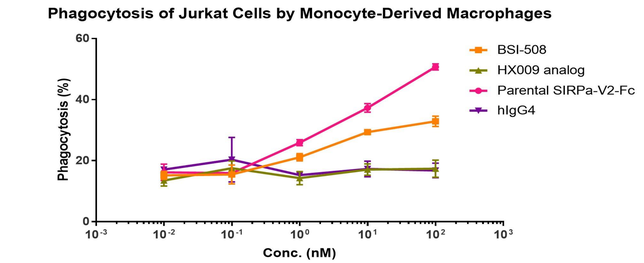
Ligand Blocking Activities of BSI-508



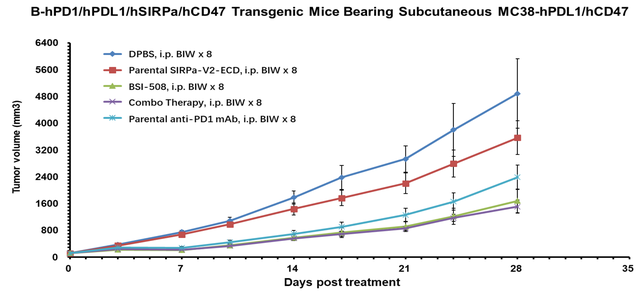
BSI-508 Maintains Bioactivity on PD1 Side



BSI-508 Maintains Bioactivity on CD47 Side



BSI-508 Shows Anti-Tumor Activity *In Vivo*



Conclusions

- BSI-508 is a novel bispecific molecule simultaneously targeting PD1 and CD47, facilitating dual blockade of PD1/PDL1 and SIRPα/CD47 signaling pathways;
- BSI-508 shows potent *in vivo* anti-tumor efficacy in B-hPD1/hPDL1/hSIRPα/hCD47 mice bearing B-hPDL1/hCD47 MC38 tumors;
- BSI-508 is a favorable asset ready for CMC development and IND-enabling studies.