BSI-507, a First-in-Class Bispecific Antibody Targeting PD1 and PVRIG for Cancer Immunotherapy

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Abstract

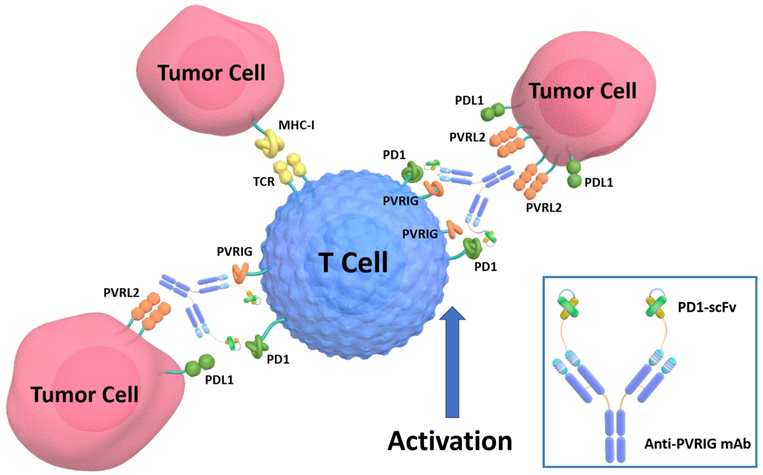
Introduction: Despite the success of anti-PD1/PDL1 therapies, only a small fraction of patients benefit from these checkpoint inhibitors (CPIs). Novel approaches to improve outcomes for patients who are resistant to current CPIs are needed. PVRIG is expressed on $CD4^+$ and $CD8^+$ T cells, NKT and NK cells. PVRIG binds with high affinity with its ligand PVRL2, which is expressed on tumor cells and some myeloid cells. The PVRIG-PVRL2 axis exerts an inhibitory effect on the cytotoxic activity of lymphocytes. Bispecific antibodies that exhibit dual blockade of PD1 and PVRIG provide a promising strategy to enhance anti-tumor immune response.

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. An anti-PVRIG mAb was identified from rats immunized with recombinant PVRIG-ECD-Fc and screened by the H^3 platform. Both anti-PD1 and anti-PVRIG antibodies were humanized, and the anti-PD1 scFv was fused to the N-terminus of the heavy chain of the anti-PVRIG antibody via a flexible linker. The binding activities and affinities were evaluated by ELISA, FACS and SPR, and the ligand blocking activities were measured by ELISA and FACS. Cell-based reporter assays were used to evaluate the functions of the anti-PD1 and anti-PVRIG mAbs alone and the bispecific antibody. In addition, the activity of the bispecific antibody to reverse PD1 and PVRIG mediated suppression of CMV $pp65_{495\text{-}503}$ antigen specific $CD8^+$ T-cell cytotoxicity was evaluated.

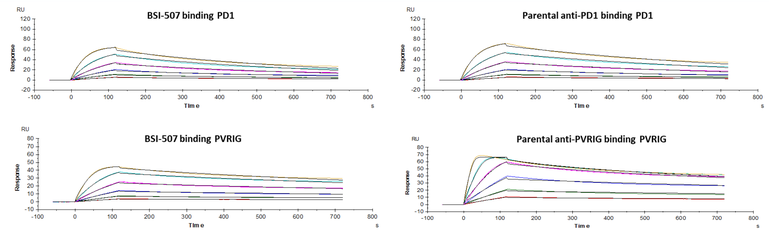
Results: BSI-507, an anti-PD1 x anti-PVRIG bispecific antibody demonstrated comparable activity to the parental anti-PD1 antibody regarding PD1 binding and PD1/PDL1 blocking. It also exhibited comparable activity to the parental anti-PVRIG antibody in PVRIG binding and PVRIG/PVRL2 blocking. Based on cell-based reporter assays, BSI-507 was able to reverse either PD1 or PVRIG mediated T-cell suppression and exhibited comparable potency to the parental antibodies. BSI-507 was also able to show enhanced reversal of both PD1 and PVRIG mediated T-cell suppression, much better than anti-PD1 or anti-PVRIG alone. In addition, BSI-507 showed the ability to reverse PD1 and PVRIG mediated suppression of CMV $pp65_{495\text{-}503}$ antigen specific $CD8^+$ T-cell cytotoxicity, stronger than either the anti-PD1 or anti-PVRIG monoclonal antibody.

Summary: BSI-507 is a first-in-class anti-PD1 x anti-PVRIG bispecific antibody for dual blockade of PD1 and PVRIG pathways to enhance reversal of T cell inhibition. BSI-507 demonstrates favorable biophysical and functional characteristics, supporting the initiation of development activities including manufacturing and IND-enabling studies.

The Dual Blockade of the PD1/PDL1 and PVRIG/PVRL2 Pathway

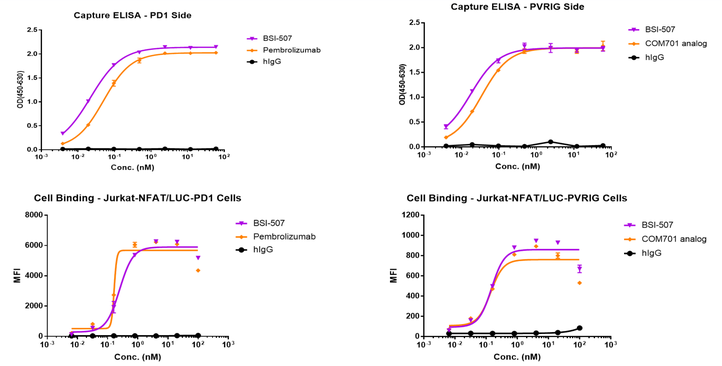


Binding Affinities of BSI-507 to PD1 and PVRIG

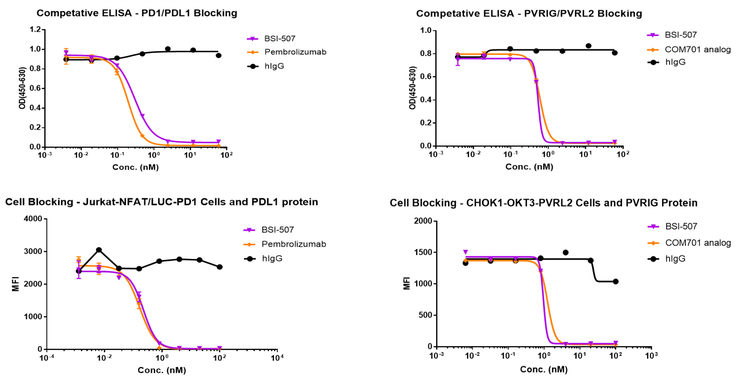


Antibody	Human PD1			Human PVRIG		
	ka (1/Ms)	kd (1/s)	K_D (M)	ka (1/Ms)	kd (1/s)	K_D (M)
BSI-507	3.94E+05	1.76E-03	4.46E-09	4.51E+06	8.84E-04	1.96E-10
Parental Anti-PD1	1.66E+05	1.23E-03	7.37E-09	/	/	/
Parental Anti-PVRIG	/	/	/	1.02E+07	1.41E-03	1.39E-10

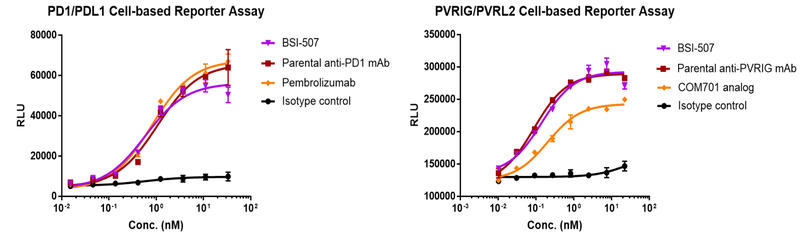
Binding Activities of BSI-507 to PD1 and PVRIG



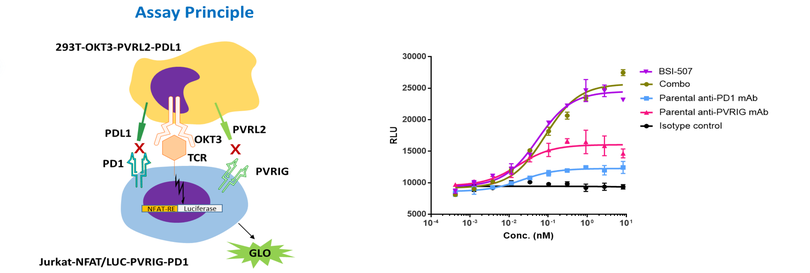
Ligand Blocking Activities of BSI-507



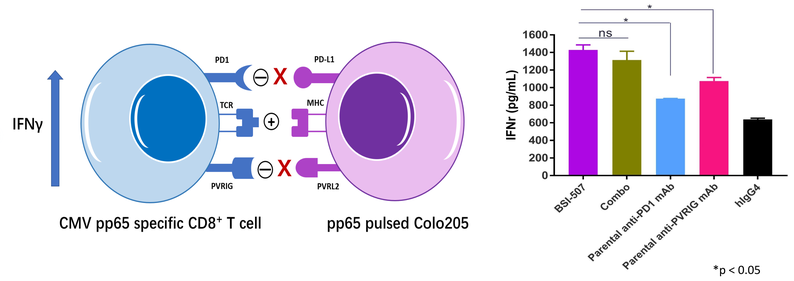
BSI-507 Maintains Bioactivity on either PD1 or PVRIG Side



BSI-507 Exhibits Dual Blockade of PD1 and PVRIG Signaling



BSI-507 Strongly Induces CMV Specific $CD8^+$ T-Cell Cytotoxicity



Conclusions

- ☐ BSI-507 is a first-in-class bispecific antibody simultaneously targeting PD1 and PVRIG, facilitating dual blockade of PD1 and PVRIG signaling pathways;
- ☐ BSI-507 shows synergistic activity on reversal of both PD1 and PVRIG mediated T-cell suppression in cell-based functional assays;
- ☐ BSI-507 is a favorable asset ready for CMC development and IND-enabling studies.