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SGN-BB228 IS A FIRST-IN-CLASS CD228-TARGETED COSTIMULATORY ANTIBODY ANTICALIN[®] BISPECIFIC DELIVERING POTENT AND CONDITIONAL 4-1BB COSTIMULATION TO TUMOR-SPECIFIC T CELLS

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Background Agonist antibodies targeting 4-1BB (CD137) effectively costimulate cytotoxic T cells and are active in preclinical models of cancer. However, clinical development of these agents has been hampered by limited efficacy and/or poor tolerability at active doses.^{1,2} To overcome the efficacy and safety limitations of this approach, SGN-BB228, a first-in-class, investigational CD228/4-1BB Antibody Anticalin[®] bispecific was created. SGN-BB228 targets CD228 (melanotransferrin, p97), a glycosylphosphatidylinositol-anchored membrane protein with limited normal tissue expression, but high and prevalent expression in melanoma, mesothelioma, lung cancer and other tumor types.^{3,4} SGN-BB228 is designed to provide a potent costimulatory bridge between tumor-specific T cells and tumor cells, improving and constraining T cell mediated cytotoxicity to tumors, potentially expanding the therapeutic window for 4-1BB agonism.

Methods Here we describe the expression profile of CD228 in cancer and normal tissues and preclinical activity of SGN-BB228 across reporter cell and primary T cell-based assays.

Results SGN-BB228 is comprised of a hinge-stabilized (S228P), Fc-null (FALA) fully human IgG4 antibody specific for CD228 connected to 4-1BB-targeting Anticalin[®] proteins⁵ via C-terminal heavy-chain fusions. The proposed mechanism of action (MOA) for SGN-BB228 is CD228-conditional clustering of 4-1BB on antigen experienced tumor-specific T cells, resulting in enhanced activation and cellular cytotoxicity. Expression analysis across cancer and normal tissues demonstrates CD228 is a tumor associated antigen prevalent in melanoma, mesothelioma, lung cancer and other tumor types with minimal normal tissue expression. Preclinical testing of SGN-BB228 in vitro shows potent CD228-conditional 4-1BB stimulation and cytotoxic T cell activation across a range of assay systems. In the presence of CD228-expressing tumor cells, but not CD228-negative tumor cells, SGN-BB228 drove dose-dependent amplification of NFκB signaling using a 4-1BB reporter cell system. SGN-BB228 also consistently drove potent CD228-conditional costimulatory activity in assays using primary T cells or whole peripheral blood mononuclear cells (PBMCs) receiving different forms of T cell receptor stimulation. The CD228-conditional activity of SGN-BB228 consistently outperformed a clinical benchmark antibody, even in the presence of antibody-clustering FcγRs expressed by PBMC. **Conclusions** Together these data introduce SGN-BB228, a first-in-class, investigational CD228/4-1BB costimulatory Antibody Anticalin[®] bispecific with potent and CD228-conditional 4-1BB costimulatory activity with therapeutic potential in multiple solid tumor types. These data support future clinical study of SGN-BB228 in a first-in-human Phase 1 trial.

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