Background V-domain Ig Suppressor of T-cell Activation (VISTA) is an immune-checkpoint regulator predominantly expressed on myeloid cells. The presence of VISTA has been shown to promote tumorigenesis and induce an immunosuppressive environment within the tumor microenvironment (TME). Moreover, VISTA’s upregulation has been associated with acquired resistance to anti-CTLA-4 and anti-PD-1/PD-L1 therapies. Therefore, VISTA represents a promising therapeutic target. HMBD-002 has been designed as a non-depleting, IgG4 monoclonal-antibody with high affinity and specificity to VISTA across species (human, cynomolgus monkey, and rodent). In preclinical studies, HMBD-002 significantly inhibited tumor growth, both as a monotherapy and in combination with pembrolizumab, while decreasing infiltration of suppressive-myeloid cells within the TME and thus increasing T-cell activity. In addition to VISTA expression on pro-inflammatory immune cells, examination of VISTA expression across cancer types has revealed that several malignancies, particularly triple-negative breast cancer (TNBC) and non-small cell lung cancer (NSCLC), express high levels of VISTA, thereby providing a rationale for exploring these indications in early clinical studies.

Methods This phase 1/2, open-label, multi-center, first-in-human trial is evaluating HMBD-002 as a monotherapy and in combination with pembrolizumab in patients with advanced solid tumors and is conducted in two parts. The dose-escalation cohorts (Part 1), follow a standard 3 + 3 study design, with adaptive dose-escalation increments, and weekly dosing for HMBD-002, to identify the maximum tolerated (or tested) dose (MTD) of HMBD-002 as a monotherapy, and in combination with pembrolizumab (pembrolizumab to be dosed Q3W), and to recommend doses for subsequent disease-directed studies (i.e. RP2D) as well as to determine safety, PK, and ADA. In the dose-expansion stage at the RP2D (Part 2), the antitumor activity of HMBD-002 alone or combined with pembrolizumab will be evaluated in patients with TNBC and NSCLC. Combination therapy will also be evaluated in additional VISTA-expressing malignancies. Biomarker analyses are exploratory endpoints in this clinical study and are assessed for treatment-induced immunological changes both systemically and within the TME. Longitudinal blood samples and pre and on-treatment tumor tissue samples will be assessed using CyTOF, multiplex-cytokine analysis, VISTA & PD-L1 IHC, and gene-expression profiling. Identification of immunological parameters associated with HMBD-002 monotherapy and combination therapy may provide insight into markers associated with the biological activity of HMBD-002. Exploratory correlative analyses with clinical outcomes may lead to the identification of predictive biomarkers of clinical benefit with HMBD-002.

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Ethics Approval The study obtained approval from the following institutional review boards: MDACC- (ID/2021-0434), Yale (ID/20214330), Stanford (ID/63175), Cedars-Sinai (ID/STUDY00001841), UTSW Medical Center (ID/STU-2021-1161), BAYLOR COLLEGE OF MEDICINE (ID/H-51228).

All participants in the trial gave informed consent before taking part in the trial.