

A PHASE 1 FIRST IN HUMAN STUDY OF HMBD-002, AN IGG4 MONOCLONAL ANTIBODY TARGETING VISTA, AS A MONOTHERAPY AND COMBINED WITH PEMBROLIZUMAB IN PATIENTS WITH ADVANCED SOLID MALIGNANCIES

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Background V-domain Ig suppressor of T cell Activation (VISTA), an immune checkpoint regulator predominantly expressed on myeloid cells, represents a promising therapeutic target due to its role in suppressing pro-inflammatory, anti-tumor responses within the tumor microenvironment (TME). Based on VISTA's broad expression across immune cell subtypes, 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) that has the ability to block a predicted counter-structure binding site. 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 increasing T cell activity. While rapid serum clearance and immune toxicities (e.g. cytokine release syndrome) have been reported for IgG1 antibodies, these were not observed preclinically with HMBD-002. In addition to VISTA expression on pro-inflammatory immune cells, examination of VISTA expression across cancer types has revealed that several malignancies, particularly human samples of 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 clinical studies.

Methods This Phase 1, first in human study is being conducted in two parts and will evaluate multiple doses and schedules of intravenously (IV) administered HMBD-002, with or without pembrolizumab, in patients with advanced solid tumors. Part 1 (dose escalation) seeks to identify the maximum tolerated dose (MTD), or the maximum tested dose, of HMBD-002 as a monotherapy, and separately, in combination with pembrolizumab to define the recommend doses for subsequent disease directed studies (i.e., recommended phase 2 dose [RP2D]). Part 2 (dose expansion) will assess the anti-cancer activity of HMBD-002 as a monotherapy at the RP2D in previously treated patients with TNBC, and NSCLC, and in combination with pembrolizumab in patients with TNBC, NSCLC, and other VISTA-expressing malignancies. The size of the disease-directed cohorts will be determined based on an interim futility analysis conducted upon enrollment of 15 patients. Safety, efficacy, pharmacokinetic, and pharmacodynamic endpoints will be monitored and reported. Correlative studies will assess pre- and post-treatment markers of immune activity in the periphery and the tumor microenvironment.

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Ethics Approval The study was approved by each participating Institution's Institutional Review Board.

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