**TPS2664: A Phase 1 First-in-Human Clinical Trial of HMBD-002, an IgG4 Monoclonal Antibody Targeting VISTA, in Advanced Solid Tumors**

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**Background**

V-domain Ig Suppressor of T-cell Activation (VISTA), is an immune checkpoint regulator found on tumor, myeloid, and other immune cells. Its presence has been shown to enhance tumor growth and create an immunosuppressive microenvironment, and may potentially contribute to developing resistance to anti-CTLA-4 and anti-PD-1/PD-L1 therapies. Therefore, VISTA represents a promising therapeutic target. HMBD-002, a non-depleting, high-affinity IgG4 monoclonal antibody against VISTA, has demonstrated significant inhibition of tumor growth in preclinical studies, both as a monotherapy and in combination with pembrolizumab. HMBD-002 acts by increasing T-cell activity and reprogramming the suppressive tumor microenvironment to a proinflammatory antitumor phenotype. Cancer types including triple-negative breast cancer (TNBC) and non-small cell lung cancer (NSCLC), which exhibit high expression levels of VISTA in the TME, provide a promising therapeutic target. HMBD-002, a non-depleting, high-affinity IgG4 antibody, has reduced backscatch with IgG4 backbone.

**Endpoints**

For HMBD-002 monotherapy and in combination with pembrolizumab

- **Primary**
  - Safety & Tolerability
  - MTX
  - RP2D

- **Secondary**
  - PK (Cmax, AUC, CL)
  - Immunogenicity
  - Preliminary antitumor activity (ORR, DoR, PFS, OS)

- **Exploratory**
  - Blood and tissue biomarkers for HMBD-002 efficacy

**Bioanalytical and Biomarker Plan**

For HMBD-002 monotherapy and in combination with pembrolizumab

- Pharmacokinetics (PK) & Anti-drug Abs (ADA)
  - Patient safety and drug clearance

- Cytokine analysis
  - Serum cytokine (INFγ, IL10, IL12p70, IL13, IL1β, IL4, IL6, IL8, TNFα)

- CyTOF analysis
  - Changes to immune cells and their phenotypes, including suppressive myeloid cells in peripheral blood mononuclear cells (PBMCs)

- Immuno-histochemistry (IHC)
  - Changes in the tumor immune microenvironment, for example, PD-L1 and VISTA expression in pre- and post-treatment tumor tissues from dose escalation and expansion cohorts

**Summary**

**Key Features & Preclinical Findings**

- No evidence of CRS observed in preclinical models nor in human MLR studies
- Strong efficacy across PDX and CDX tumor models
- Robust evidence of immune stimulation as a preclinical PD biomarker

**Status of Trial in Progress**

- Monotherapy cohorts 1 through 4 have been completed without DLT
- Currently enrolling monotherapy Cohort 5
- Projected to enroll first patient of combination therapy H2 2023
- Exploratory biomarker endpoints to assess pharmacodynamic changes are being evaluated

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**References**


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A Study of HMBD-002, a Monoclonal Antibody Targeting VISTA, as Monotherapy and Combined With Pembrolizumab
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