

## **The Curis-Sponsored 2<sup>nd</sup> Annual VISTA Symposium Offers New Insights into the VISTA Checkpoint as a Unique Target for Immunotherapy**

*Global leaders in immuno-oncology discussed VISTA's roles in cancer immunology, as well as the latest advances in the development of therapeutics that target VISTA.*

*Emerging research demonstrates key distinct roles for VISTA in the regulation of the immune system and shaping the tumor microenvironment, suggesting intriguing potential as a drug target.*

Curis, Inc. (NASDAQ: CRIS), a biotechnology company focused on the development of innovative therapeutics for the treatment of cancer, sponsored a successful 2<sup>nd</sup> Annual VISTA Symposium, held virtually on September 23, 2022, and hosted by Randolph Noelle, Ph.D., Active Emeritus Professor of Microbiology and Immunology, Norris Cotton Cancer Center, Geisel School of Medicine at Dartmouth.

V-type immunoglobulin domain-containing suppressor of T cell activation (VISTA) is a negative checkpoint regulator representing a new and differentiated target for immunotherapy. VISTA is expressed on immune cells and plays an important role in the regulation of the immune system; elevated levels of VISTA are associated with many human cancers and correlate with poorer outcomes. Potential treatments that target VISTA have shown promise in multiple preclinical tumor models and are currently being assessed in phase 1 clinical trials.

Highlights of the 2<sup>nd</sup> Annual VISTA Symposium included:

### **New Insights into VISTA Biology**

After opening the meeting, Dr. Randolph Noelle (Dartmouth) described the important role VISTA serves in immune regulation by sharing compelling preclinical research demonstrating that deleting VISTA results in a loss of quiescence by resting CD4<sup>+</sup> T cells, promotes pro-inflammatory responses by memory T cells, and enhances autoimmunity.

Dr. Sam Lee (Yale) followed with novel research on potential binding partners for checkpoint inhibitors, particularly VISTA, and highlighted preclinical research on the immune suppressive effects of VISTA expression on myeloid-derived suppressor cells (MDSCs) within the tumor microenvironment.

### **The Role of VISTA in Tumor Immune Evasion**

Dr. Louise Lines (Dartmouth) presented preclinical research emphasizing the mechanisms by which anti-VISTA antibodies impact tumors and distinguished the effects of targeting VISTA from agents targeting PD-1 or CTLA-4. In preclinical cancer models, anti-VISTA treatment improves immune cell density in tumors, stimulates myeloid cell activation and antigen presentation, and reduces the suppressive effects of myeloid cells on infiltrating T cells.

### **VISTA Targeting**

Dr. Lionel Lewis (Dartmouth) provided an overview of target-mediated drug disposition where a drug binds with such high affinity to its target that it impacts the drug's pharmacokinetics, how it affects the

dosing of several anti-checkpoint inhibitor antibodies, and why it may influence the dosing of anti-VISTA antibodies currently in development.

Dr. Andrew Scott (University of Melbourne) gave compelling evidence demonstrating that radiolabeled anti-VISTA antibody CI-8993 (Curis) localizes specifically to tumors in a humanized mouse model and that CI-8993 saturates the VISTA receptor at high doses.

### **Clinical Opportunities for Targeting VISTA**

Dr. Kathleen Mahoney (Harvard Medical School) highlighted the potential for targeting VISTA in kidney cancer, where it is known that VISTA is highly expressed on tumor-infiltrating immune cells and can be expressed by some tumor cells.

Dr. Dhanya Nambiar (Stanford) presented promising data on the synergistic impacts of radiotherapy and anti-VISTA treatment in preclinical models of head and neck cancer. Anti-VISTA treatment induced anti-tumor immune responses and reduced radiotherapy-induced migration of MDSCs to the tumor.

Dr. Matthew Vesely (Yale) shared emerging research that tumor-infiltrating myeloid cells associated with melanoma and cutaneous squamous cell carcinoma have high levels of VISTA expression. In both cases, VISTA expression did not correlate with PD-L1 expression, and in patients with melanoma, VISTA expression on myeloid cells correlated with recurrence and poorer overall survival.

### **Anti-VISTA Therapeutic Strategies**

Robert Martell (Curis, Inc.) gave an overview of the clinical development of CI-8993, the first anti-VISTA monoclonal antibody (mAb) to be studied in a clinical trial. Currently being assessed in a phase 1 dose-escalation study, CI-8993 has demonstrated a favorable pharmacokinetic profile and has shown pharmacodynamic effects on multiple anti-tumor mechanisms, including reduced recruitment of MDSCs and increased antigen presentation, natural killer (NK) cell maturation, and release of T cell activating factors.

Jerome Boyd-Kirkup (Hummingbird Bioscience) summarized the development of HMBD-002, a rationally designed anti-VISTA mAb currently being assessed in a phase 1a dose-escalation trial. In preclinical models, HMBD-002 inhibited tumor growth by impacting the tumor microenvironment, including enhanced CD8<sup>+</sup> T cell activation and reprogramming and activating tumor-associated macrophages.

Thierry Guillaudeux (Kineta, Inc.) reviewed the development of KVA12.1, an anti-VISTA mAb that binds a unique epitope. In preclinical models, KVA12.1 impacted the tumor microenvironment through reduced MDSC suppression of T cells and increased activation of monocytes, NK cells, and T cells. KVA12.1 has been well-tolerated in non-human primate toxicology studies, and a phase 1 dose-escalation study is planned.

### **Summary**

These presentations captured the excitement among researchers at the progress made in understanding and targeting the VISTA checkpoint. A consistent theme across the preclinical research in tumor models

was that VISTA inhibition relieved myeloid suppression, increased activation of myeloid and T cells, and promoted pro-inflammatory changes in the tumor microenvironment. Notably, the clinical potential of VISTA inhibition was reflected in presentations on three different anti-VISTA mAb therapies being assessed in active or planned phase 1 clinical trials. Future VISTA Symposia may offer further expert insights into the mechanisms and clinical profile of VISTA inhibition in cancer treatment.