KVA12.1: AN ANTI-VISTA MONOCLONAL ANTIBODY WITH STRONG SINGLE AGENT ANTI-TUMOR ACTIVITY AND NO EVIDENCE OF CYTOKINE MEDIATED TOXICITY

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Background V-domain Immunoglobulin Suppressor of T cell Activation (VISTA), an immune checkpoint regulator, is highly expressed in myeloid cells in the tumor microenvironment (TME). It has been shown in vitro and in vivo that VISTA inhibits T cell activation and prevent T cell recruitment into tumors. In patients, high VISTA expression is associated with poor prognosis and is also a potential mediator of resistance to current checkpoint therapies. VISTA is a very attractive new target for cancer immunotherapy.

Methods Kineta has developed a clinical candidate anti-VISTA monoclonal antibody, KVA12.1, which demonstrates in human VISTA KI mice strong anti-tumor activities as a single agent and in combination with other check-point inhibitors in multiple syngenic tumor models. KVA12.1 is an IgG1 antibody targeting a unique epitope on VISTA that has been engineered to extend its half-life and reduce its immunoreactivity. These modifications introduced in the IgG1 backbone of the antibody could prevent possible adverse events related to a Cytokine Release Syndrome (CRS) when injected into cancer patients.

Results We show here that the engineered IgG1 of KVA12.1 increases binding of the antibody to neonatal Fc-Receptor compared to the wild type IgG1 and reduces the binding to different FcRg receptors in particular FcgRIIIa involved in a strong immunoreactivity. We have also shown in previous work that KVA12.1 binds with the same potency and specificity to human and Non-human primate (NHP) VISTA. We have therefore conducted Non-GLP and GLP toxicological studies and demonstrated that KVA12.1 is very well tolerated in NHP, even after multiple high dose injections over a one-month period. No mortality or overt clinical signs have been observed, as well as no treatment-related findings for clinical pathology endpoints and no change of CRS cytokine levels, in particular IL6 and TNFa. The absence of CRS markers has also been confirmed in whole blood obtained from multiple healthy donors. Besides, we have confirmed in these same NHP studies the extended PK of our antibody. KVA12.1 will be tested in a clinical trial in cancer patients with advanced solid tumors that have failed previous therapies with current standard of care. To guide our inclusion criteria, VISTA expression has been evaluated by immunohistochemistry on a large panel of human cancer tissue samples.

Conclusions The clinical trial will start by the end of 2022 and will evaluate the safety and tolerability of KVA12.1 injected alone or in combination with pembrolizumab, as well as the Recommended Phase 2 dose (RP2D) or maximum tolerated dose (MTD) as a primary objective. Pharmacokinetics, immunogenicity and tumor responses will also be evaluated in this trial.