Background Multiple cancer immunotherapies of T-cell checkpoint inhibitors have been approved worldwide. However, most patients with advanced solid tumors do not benefit, or relapse after T-cell checkpoint blockade. Myeloid checkpoint inhibition is a new approach to cancer immunotherapy. V-domain Ig Suppressor of T-cell Activation (VISTA), a promising therapeutic target, is an immune checkpoint primarily expressed by myeloid cells. Its expression in tumors is associated with high myeloid infiltration. Its presence is clearly associated with an immunosuppressive tumor microenvironment, and it may contribute to resistance to anti-CTLA-4 and anti-PD-1(L)1 therapies.

KVA12123, an engineered IgG1 fully human monoclonal antibody, specifically binds to VISTA with high affinity and blocks VISTA interactions with its ligands. In vitro, KVA12123 increases pro-inflammatory responses and enhances antigen presenting cell phenotypes. In vivo, it exhibits strong single agent anti-tumor activity amplified in combination with anti-PD1 in multiple tumor models. Toxicology studies performed in cynomolgus monkeys at doses up to 100 mg/kg administered intravenously once weekly for a total of 4 doses showed that KVA12123 was well-tolerated at all dose levels.

Methods The no-observed-adverse-effect-level (NOAEL) of 100 mg/kg in NHP provides a safety margin for KVA12123 administration to humans at a starting dose of 3 mg, which was derived using receptor occupancy and a MABEL (minimum anticipated biological effect level) approach. This trial is a first-in-human, Phase 1/2, multicenter, open-label, dose-escalation, safety, pharmacokinetic (PK), and pharmacodynamic evaluation of intravenously administered KVA12123, both as monotherapy and in combination with pembrolizumab, in adult patients with solid tumors that have failed standard of care therapies (NCT05708950). Up to 60 patients will be enrolled in the Phase 1 of the study. KVA12123 is administered every 2 weeks at escalating doses over a 6-week cycle and pembrolizumab every 6 weeks at a 400mg fixed dose in the combination arm. The dose-limiting toxicity (DLT) evaluation period is 21 days.

Results Safety, PK, clinical activity using iRECIST and exploratory biomarkers are evaluated in this trial. Preliminary results will be presented. The primary objective of the study is to assess safety and tolerability at increasing dose levels of KVA12123 in successive cohorts of adult patients (alone and in combination with pembrolizumab) with advanced relapsed or refractory solid tumors, to estimate the maximal tolerated dose (MTD) or select the recommended phase 2 doses (RP2Ds). Secondary objectives include characterizing PK, immunogenicity, and preliminary anti-tumor activity. Biomarker evaluation includes receptor occupancy, changes in immune cell markers and VISTA expression on collected biopsies.

Trial Registration NCT05708950

Ethics Approval Institutional review boards’ approval is requested and obtained from each of the 10 clinical sites engaged in this Phase 1/2 clinical trial. Informed consents are collected for every patient enrolled in the trial.

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