ANALYSIS OF THERAPEUTIC EFFECT AND SAFETY OF PD-1 INHIBITORS IN CLINICAL TREATMENT OF ORAL AND MAXILLOFACIAL MALIGNANT TUMORS

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Background As the sixth largest cancer in the world, the recurrence rate and metastasis rate of oral cancer are relatively high. Although the incidence of oral cancer has decreased in the past decade, the overall survival rate has only increased by 5%. The 5-year survival rate of early oral squamous cell carcinoma is only 50% to 60%. PD-1 inhibitors can bind to programmed death molecule 1 (PD-1) and block its binding to programmed death molecule ligand 1 (PD-L1), so as to restore immune function and achieve anti-tumor effect.

Methods 33 patients with oral malignant tumors were selected from the Department of Maxillofacial surgery of the first affiliated Hospital of Zhengzhou University from August 2019 to June 2020. Among them, 8 patients were only treated with PD-1 inhibitor Camrelizumab injection combined with the targeted drug apatinib. 25 patients were treated with PD-1 inhibitor Camrelizumab injection combined with targeted drug apatinib after the operation. The dose of PD-1 inhibitor was 200 mg by intravenous infusion every three weeks, and the dose of apatinib was daily 500 mg orally. The duration of treatment with PD-1 inhibitors combined with apatinib ranged from 1 month to 10 months. The survival status and related immune adverse reactions of patients after one year of treatment were followed up and evaluated.

Results For 33 patients enrolled in the study, after excluding the cessation of PD-1 inhibitor treatment due to a variety of reasons, the overall disease control rate was 80.0%, of which 3 patients developed further and died. Other relevant data need to be further tracked because they have not reached the end point of observation. Among the 33 patients, 5 patients had immune-related adverse reactions (15.2%), including 2 cases of skin rash, 1 case of skin capillary hyperplasia and 2 cases of other adverse reactions.

Conclusions The patients with Oral malignant tumor treated with PD-1 inhibitor Camrelizumab injection combined with targeted drug apatinib or postoperative adjuvant therapy can effectively control tumor development, improve the survival of patients, and help to improve the stability of postoperative efficacy.

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OVERCOMING IMMUNOTHERAPY RESISTANCE IN T CELL-INFLAMED LUNG CANCER

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Background Tumor infiltrating T cells (TIL) are highly correlated with response to checkpoint blockade immunotherapy (CBT) in melanoma. However, in non-small cell lung cancer (NSCLC), 61% of patients have TIL, but only 32% respond to CBT. It is unknown how these T cell-inflamed tumors are resistant to CBT. Understanding and overcoming this resistance would greatly increase the number of cancer patients who benefit from CBT.

Methods To understand lung-specific anti-tumor immune responses, a NSCLC cell line derived from an autochthonous murine lung cancer (KP cell line) was transplanted into syngeneic C57BL/6 mice subcutaneously or intravenously. To study antigen-specific responses, the KP cell line was engineered with SIY and 2C TCR transgenic T cells, which are specific for SIY, were adoptively transferred into tumor-bearing animals.

Results Subcutaneous KP tumors responded to CBT (aCTLA-4 and aPD-L1) with significant tumor regression while lung KP tumors were CBT resistant. Immunohistochemistry found that this was not due to lack of T cell infiltration, as lung tumors contained 10-fold higher numbers of CD8+ TIL than subcutaneous tumors. Single cell RNA sequencing of TIL uncovered that CD8+ TIL in lung lesions had blunted effector molecule expression that correlated with a lack of IL-2 signaling. Adaptive transfer of naïve, tumor-reactive 2C T cells resulted in benefit from CBT.

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HIGHLY POTENT FULLY HUMAN ANTI-VISTA ANTIBODIES – A NEW TARGET CHECKPOINT INHIBITOR AGAINST IMMUNOSUPPRESSIVE MYELOID CELLS


Background V-domain Immunoglobulin Suppressor of T cell Activation (VISTA/PD-1H) is a B7 family ligand expressed on circulating and intratumoural myeloid cells as well as Treg and NK cells. It has been shown to inhibit T cell responses to anti-CTLA-4 and anti-PD1 therapies and therefore is a valuable new target for cancer immunotherapy.

Methods Kineta has analyzed 107 fully human ScFv antibodies directed against VISTA.

Results Our lead candidates exhibit high potencies in the sub-nanomolar range and are also characterized by a long kDis. They specifically target human and cynomolgous monkey VISTA on a singular unique epitope. In a Staphylococcus Enterotoxin B T-cell activation assay, Kineta’s anti-VISTA antibodies efficiently induce IFNγ secretion. They also promote strong maturation of Antigen Presenting Cells with an increase of CD80 and HLA-DR surface expression as well as CXCL10 secretion. The mechanism of action is mediated in part by NK cells. We demonstrated that myeloid cells acquire a high level of VISTA expression during MDSC or M2 differentiation in vitro and that Kineta’s anti-VISTA antibodies prevent the differentiation of MDSC as well as their immunosuppressive activity against T cells. Anti-VISTA antibodies mediate single-agent antitumor effects in syngeneic tumor models in wild-type mice and show enhanced activity in combination with anti-PD1 and anti-CTLA-4 treatment. Candidate anti-VISTA antibodies have also been evaluated in exploratory tolerability and PK studies in cynomolgous monkey. These studies demonstrated that multiple weekly doses of antibodies are well-tolerated with appropriate PK for lead selection and optimization.

Conclusions Our results strongly favor further characterization and continued development of selected lead antibodies for the potential treatment of colder, less immunogenic tumors.

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