ANALYSIS OF THERAPEUTIC EFFECT AND SAFETY OF PD-1 INHIBITORS IN CLINICAL TREATMENT OF ORAL AND MAXILLOFACIAL MALIGNANT TUMORS
Haochuan Liu*, Yaqiong Jie, Xinguang Han. The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

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 1 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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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 intratumoral myeloid cells as well as Treg and NK cells. It has been shown to inhibit T cell responses in vitro and in preclinical models. In patients, VISTA is also a potential mediator of resistance 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 cynomolgus 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 cynomolgus 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.

183 OVERCOMING IMMUNOTHERAPY RESISTANCE IN T CELL-INFLAMED LUNG CANCER
Brendan Horton*, Brendan Horton, Duncan Morgan, Noor Momin, Vidit Bhandarkar, Dane Wittrup, Chris Love, Stefani Spranger. Massachusetts Institute of Technology, Cambridge, MA, USA

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. Adoptive transfer of naïve, tumor-reactive 2C T cells resulted in...
equally robust T cell proliferation in both the inguinal and mediastinal lymph nodes (LNs). However, RNA sequencing of adoptively transferred 2C T cells isolated 3-days after transfer from draining LNs identified that T cells activated in the mediastinal LN had reduced levels of IL-2 signaling and blunted effector functions early during priming. Flow cytometry confirmed that T cells primed in the mediastinal LNs did not express CD25, GZMB, or IFN-g, while T cells in inguinal LNs upregulated all three of these effector molecules. Delivery of IL-2 and IL-12 during priming was sufficient to restore effector molecule expression on 2C T cells in mediastinal LNs. Analysis of published patient data identified that a subset of lung cancer patients showed a sizable population of CD8+ TIL with low IL-2 signaling and low expression of effector molecules, including common targets of CBT.

Conclusions Immunotherapy resistance in T cell-inflamed tumors is due to defective CD8+ T cell effector differentiation. IL-2-based therapies could enhance differentiation of functional CD8+ effector T cells and could turn immunotherapy-resistant tumors to immunotherapy sensitive tumors. This is the first mechanistic study providing evidence for a distinct type of T cell dysfunction resistant to current CBT.

Ethics Approval This study was approved by MIT’s Committee on Animal Care, protocol number 0220-006-23.

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184 TWO TYPES OF ANTI-TIGIT ANTIBODIES WITH DISTINCT BINDING EPITOPE AND FUNCTIONAL ACTIVITIES

Tingting Zhong, Xinghua Pang, Zhaoliang Huang, Na Chen*, Xiaoping Jin, Yu Xia, Maxwell Zhongmin Wang, Baiyong Li.

Background TIGIT is an inhibitory receptor mainly expressed on natural killer (NK) cells, CD8+ T cells, CD4+ T cells and Treg cells. TIGIT competes with CD226 for binding with CD155. In cancers, CD155 has been reported to up-regulate on tumor cells, and TIGIT was found to increase on TILs. Activation of TIGIT/CD155 pathway would mediate immunosuppression in tumor; while blockade of TIGIT promotes anti-tumor immune response.

Methods AK126 and AK113 are two humanized anti-human TIGIT monoclonal antibodies developed by AkesoBio. Binding activity of AK126 and AK113 to human TIGIT, and competitive binding activity with CD155 and CD112, were performed by using ELISA, Fortebio, and FACS assays. Cross-reactivity with cognomolus monkey TIGIT and epitope binning were also tested by ELISA assay. In-vitro assay to investigate the activity to promote IL-2 secretion was performed in mixed-culture of Jurkat-TIGIT cells and TPH-1 cells.

Results AK126 and AK113 could specifically bind to human TIGIT with competitive affinity and effectively blocked the binding of human CD155 and CD112 to human TIGIT. X-ray crystal structure of TIGIT and PVR revealed the C-C’ loop and FG loop regions of TIGIT are the main PVR interaction regions. The only amino acid residue differences in these regions between human and monkey TIGIT are 70C and 73D. AK126 binds to both human and monkey TIGIT, AK113 binds only to monkey TIGIT. This suggests that these residues are required for AK113 binding to human TIGIT, but not required for AK126. Interestingly, results from cell-based assays indicated that AK126 and AK113 showed significantly different activity to induce IL-2 secretion in mixed-culture of Jurkat-TIGIT cells and TPH-1 cells (figure 1A and B), in which AK126 had a comparable capacity of activity to 22G2, a leading TIGIT mAb developed by another company, to induce IL-2 secretion, while, AK113 showed a significantly higher capacity than 22G2 and AK126.

Abstract 184 Figure 1 Anti-TIGIT Antibodies Rescues IL-2 Production in Vitro T-Cell Activity Assay in a dose dependent manner. Jurkat-TIGIT cells (Jurkat cells engineered to over-express human TIGIT) were co-cultured with THP-1 cells, and stimulated with plate-bound anti-CD3 mAb in the presence of TIGIT ligand CD155 (A) or CD112 (B) with anti-TIGIT antibodies. After incubated for 48h at 37° C and 5.0% CO2, IL-2 levels were assessed in culture supernatants by ELISA. Data shown as mean with SEM for n = 2.

Conclusions We discovered two distinct types of TIGIT antibodies with differences in both epitope binding and functional activity. The mechanism of action and clinical significance of these antibodies require further investigation.

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185 CAMRELIZUMAB MONOTHERAPY OR COMBINATION THERAPY IN PATIENTS WITH RECURRENT OR METASTATIC CERVICAL AND ENDOMETRIAL CARCINOMA: A RETROSPECTIVE STUDY

Hong Liu*, Shuhuai Niu, Zhaohui Fang, Xi Chen, Qianying Zhang. The Fourth Hospital of Hebei Medical University, Hebei, China

Background Patients with recurrent or metastatic cervical and endometrial carcinoma have poor prognosis and few treatment options. Blocking the interaction between PD-1 and its ligands is a promising treatment strategy. Camrelizumab is a humanised anti-programmed death-1 (anti PD-1) antibody. This study aimed to assess the anti-tumour activity and safety of camrelizumab in patients with recurrent or metastatic cervical and endometrial carcinoma.

Methods We performed a retrospective analysis for recurrent or metastatic cervical and endometrial carcinoma patients. Eligible patients were aged 28–73 years with an Eastern Cooperative Oncology Group performance status of 0 or 2. Patients received camrelizumab alone(200 mg iv d1 q2w) or in combination with chemoradiotherapy/chemotherapy. The primary endpoint was objective response (ORR). The secondary endpoints included disease control rate (DCR), median progression-free survival (mPFS) and safety.

Results A total of 21 patients were enrolled between September 20, 2019, and July 8, 2020. 18 patients were evaluated for efficacy and 21 patients were available for safety analysis.