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Methods: We have analyzed the multi-omic Glioma Longitudinal Analysis dataset, integrating DNA and RNA sequencing datasets from primary and post-treatment gliomas.

Results: We classified tumors as harboring temozolomide-associated hypermutation based on mutational burden increase (HM), and RT-associated signature based on small deletion burden increase (RTscars). By deconvoluting RNA profiles into cell state fractions, we observed an increase of a proliferating stem-like (PSL) cell state in 50% of patients with a RTscars signature which was significantly higher than RTscars-/HM—patients (P=8e-04, Fisher’s exact). PSL cell state increase associated with worse overall survival outcomes (P=1.5e-03, log-rank). We observed a significant correlation between the expression change of E2F cell cycle regulator genes (R=0.91, P=6.7e-04, Pearson) and EZH2 (R=0.81, P=8.3e-03) with the increase in the PSL cell state, nominating the E2F/EZH2-pathway as regulator of the PSL cell state. Furthermore, the RTscars signature was associated with an increase in frameshift neo-antigens and significantly higher neoantigen burden at recurrence (P=2.4e-02, Kruskal-Wallis). This was accompanied by a significantly higher post-treatment T-cell fraction in RTscars+ tumors (P=8.2e-04, Wilcoxon), suggesting an increased T-cell infiltration in these patients.

Conclusions: Our analyses revealed a longitudinal increase in the proliferating stem-like cell state associated with RT-resistance and nomimates the cell cycle pathway as an actionable target. The RT-associated deletion signature (RTscars) correlated with increased frameshift-neoantigens and T-cell fractions at recurrence, suggesting a potential benefit of a combinatorial immune-targeted therapy in this specific patient population.

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300P The clinical results of an investigator initiated trial of allogeneic CAR-T cells targeting IL13Rα2 in the treatment of high-grade glioma

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Background: Glioblastoma is the most common intracranial malignant tumors, which is difficult to treat and has poor prognosis. T cell immunotherapy is becoming a powerful strategy for the treatment of cancer and may provide an opportunity to improve the prognosis of patients with advanced glioma. This trial has three purposes: 1) to evaluate the safety and feasibility of allogeneic CAR-T cells in human body; 2) Lumbar injection and intratumoral injection were compared; 3) Preliminarily evaluate the effectiveness of our product in patients with advanced glioma.

Methods: We are developing allogeneic universal CAR-T cells for IL13Rα2 (IL13Rα2 UCAR-T cells) for the treatment of advanced glioma. This is a off-the-shelf anti-IL13Rα2 allogeneic CAR-T cells candidate product, which is made of a series of healthy donor materials, avoiding many shortcomings of autologous car-T products. We report here initial findings from our first-in-human clinical trial (ChiCTR200028801).

Results: We have treated a total of 7 patients, and the longest time after the first injection has been 21 months. The most common side effects are fever and anorexia. The significant increase of inflammatory factors such as interleukin-6 and interleukin-8 can be detected in cerebrospinal fluid, but the cytokine storm seen in the application of CAR-T cells in hematologic malignancies is not seen. Among the 7 patients, one patient had complete remission (CR) and lasted for 10 months, 4 patients had partial remission (PR), which was defined as tumor regression of more than 50%, and 2 patients had disease stability (SD). Therefore, the overall effective rate was 71.42% (5/7) and the disease control rate was 100% (7/7). The patient with the longest follow-up had survived for 18 months after the first injection. We monitored the number of IL13Rα2 UCAR-T cells in cerebrospinal fluid by flow cytometry or copy number detection. We found that our IL13Rα2 UCAR-T cells could survive in cerebrospinal fluid for more than 30 days.

Conclusions: These early clinical findings suggest that lumbar puncture delivery of allogeneic IL13Rα2 UCAR-T cells is safe and well-tolerated, and that IL13Rα2 UCAR-T cells are capable of eliciting potent antitumor responses against recurrent glioma.

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302P A multicenter, open-label, dose-escalation (DE), first-in-human study of VEGFRs and CSF1R inhibitor SYHA1813 in patients (pts) with recurrent high-grade gliomas (HGG) or advanced solid tumors

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Background: SYHA1813 is a novel small-molecule vascular endothelial growth factor receptors (VEGFRs)/colony-stimulating factor 1 receptor (CSF1R) inhibitor, exerting synergistic antitumor effects through inhibiting angiogenesis and modulating macrophage polarity in preclinical models. We report preliminary results from a phase I, DE study of SYHA1813 in pts with recurrent or advanced solid tumors including HGG.

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