Targeting MDSCs with HF1K16 Unlocks Long-Term Survival in Refractory Recurrent Glioma: an update of NCT05388487

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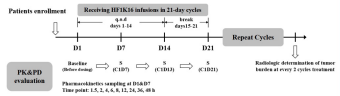
BACKGROUND

- Recurrent gliomas remain a disease of high unmet need, with limited effective therapies and progressive systemic immune exhaustion characterized by both depletion of T lymphocytes and accumulation of immunosuppressive myeloid-derived suppressor cells (MDSCs).[pt# 001]
- HF1K16 is a novel immunomodulatory therapy designed to target MDSCs through a liposomal formulation of all-trans retinoic acid (ATRA), inducing differentiation and restoring immune balance. ATRA is an endogenous bioactive molecules obtained during vitamin A metabolism. We have shown in an earlier study that it can affect MDSCs in circulation as well as in tumor tissues in solid tumor patients, by promoting maturation and differentiation of the immature myeloid cells.
- We present updated results from the ongoing Phase I study of HF1K16 (NCT05388487) in recurrent glioma patients.HF1K16 is a drug encapsulated immune modulating liposome containing all-trans retinoic acid.

METHOD

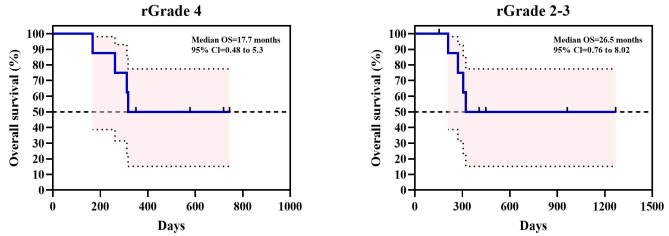
- A total of 23 patients with recurrent or refractory glioma (9 males, 14 females) were enrolled. Eligible patients had confirmed advanced disease and prior treatment failure. HF1K16 was administered in 21-day cycles (q.o.d., days 1–14). Peripheral blood mononuclear cells (PBMCs) were collected longitudinally for multiparametric flow cytometry. In some cases, surgically resected tumor tissue after treatment of therapy was analyzed using spatial flow cytometry.



RESULTS

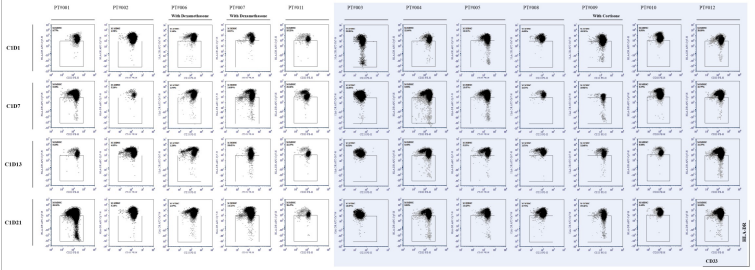
- **Patient Enrollment and Treatment:** A total of 23 patients with recurrent gliomas were screened for this trial, of whom 17 met eligibility criteria and were evaluable for efficacy . The study population included **8** patients with **recurrent grade 4 glioblastoma** and **9** patients with **recurrent grade 2–3 gliomas**.

Figure 1. HF1K16 Treatment Prolongs Survival in Patients with Recurrent Brain Tumors



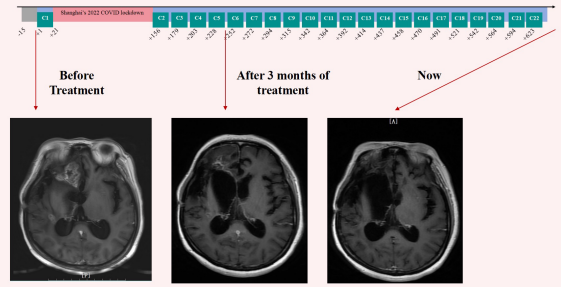
- **Survival Outcomes:** In the 8 patients with recurrent grade 4 glioblastoma, median overall survival (OS) was 17.7 months. Median OS in the 9 evaluable recurrent grade 2–3 gliomas patien was 26.5 months.

Figure 2. Reduction in circulating m-MDSC were observed in 7 of 12 patients after 3 injections of HF1K16.



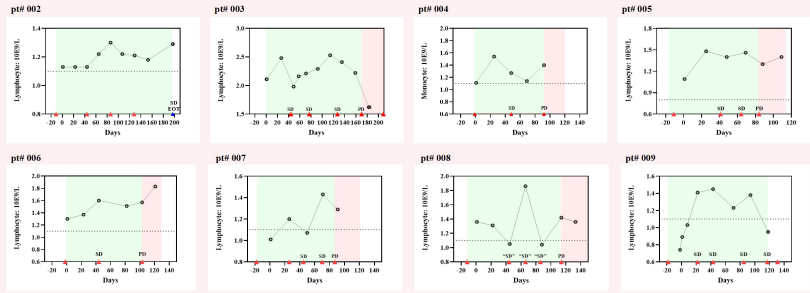
- A decreased proportion of circulating monocytic MDSCs ($CD14^+HLA\text{-}DR^-$) were seen during the treatment (from C1D1 to C1D13) in **7/12** patients. When treatment was paused for 7 days (C1D21), mMDSC proportions rebounded. Notably, the two non-responders at 90 mg/m² had documented prior dexamethasone exposure, suggesting that concurrent or antecedent corticosteroids may blunt the myeloid-modulating effect.

Figure 3. One Patient With Recurrent-Grade 2 Glioma Achieved CR After 11 Cycles of Treatment And Has Been Tumor Free For Over 2 years



- Over ~10 months of therapy, this patient's ALC climbed steadily while the tumor regressed.

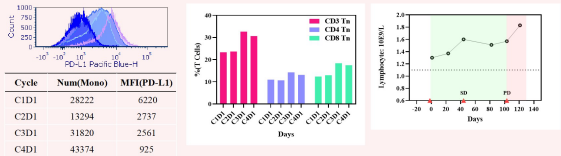
Figure 4. Changes In The Patient's Total Lymphocyte Counts During Multiple Cycles of HF1K16 Treatment.



- Many patients presented with low peripheral blood lymphocyte count at enrollment, with some even falling below the normal range (dashed line). Among those who completed multiple treatment cycles, we observed an increase in lymphocyte counts compared to pre-treatment levels

Figure 5. PBMC And Explant Tumor Tissue Analysis of A Patient (# 006) Who Have Received 4 Cycles Of HF1K16 Treatments (84 days)

- We observed progressive decrease of PD-L1 expression on the circulating monocyte.
- Concurrently, complete blood count revealed a continuous rise in absolute lymphocyte counts.
- MRI brain scan measurement indicate the disease progression after 4 cycles of treatment. Analysis of resected tumor tissure revealed marked infiltration of CD3 T lymphocytes (immunohistochemistry)



Cycle	Num(Mono)	MFI(PD-L1)
C1D1	28222	6220
C2D1	13294	2737
C3D1	31820	2561
C4D1	43374	925

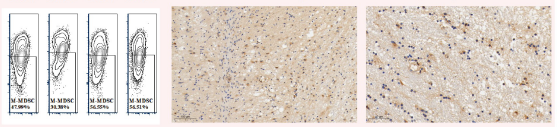
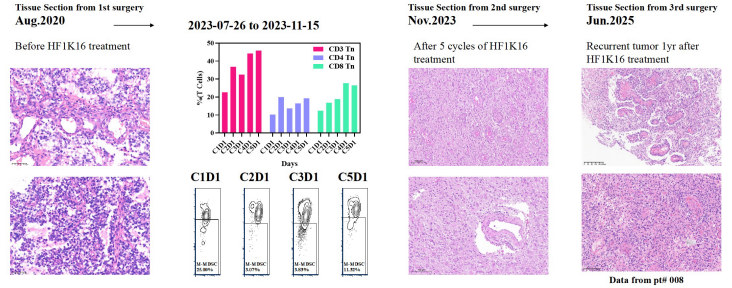
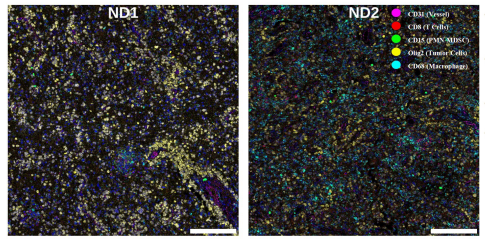


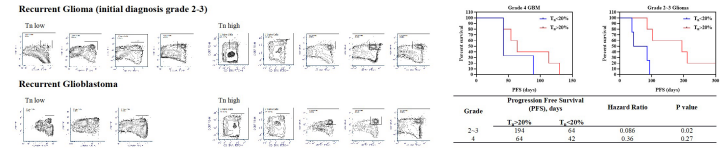
Figure 6. "Window of Opportunity" Analysis of Pt#008 Tissue Section In The Study Group





- A patient with recurrent WHO grade 4 glioblastoma received 5 cycles of HF1K16 and then progressed radiographically.
- Following the 2nd surgery, she has **remained tumor-free for 12 months without further anticancer therapy**.
- Then tumor recurred for the 2nd time and the patient received a 3rd surgery.
- Analysis of the post-HF1K16 resection revealed a T-cell –infiltrated, interaction-dense TME.

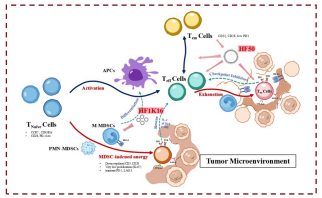
Figure 7. Higher baseline naïve T-cell proportion associates with longer PFS in HF1K16-treated recurrent glioma



- Patients were dichotomized into low (<20%) and high (≥20%) baseline Tn groups, and PFS was compared.
- For recurrent glioblastoma,median PFS was 64 days in the high Tn group versus 42 days in the low Tn group. For recurrent glioma, high Tn group had a median PFS of 194 days versus 64 days in the low Tn group .
- This result suggests that patients with higher levels of Tn might benefit more rapidly from the immunosuppression reversal induced by HF1K16.

CONCLUSION

- HF1K16 are shown to be able to exert effects on reprogramming both peripheral monocyte cells and tumor microenvironment.
- Across multiple patients, we observed both early and sustianed immune response, including reductions in immunosuppressive myloid populations and increase lymphocyte activity.
  these immune shifts were accompanied in several cases by radiographic tumor control and prolonged overall survival,
- these findings highlight the therapeutic potential of HF1K16 as a novel immunomodulatory agent in the treatment of recurrent brian tumors.



Acknowledgements & Disclosure

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- Yuhong Xu is employed and holds stocks in Hangzhou Highfield Biopharm.