1002P :A phase I study of the Myeloid-derived suppressor cells modulator HF1K16 in refractory and metastatic cancer patients: preliminary efficacy and safety.

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BACKGROUND

- Myeloid-derived suppressor cells (MDSCs) represent a significant immunosuppressive mechanism in various tumors. MDSCs are found in higher numbers in cancer patients' peripheral blood mononuclear cells (PBMCs) and in the tumor microenvironment.
- All-trans retinoic acid (ATRA) is a natural vitamin A metabolite. A substantial body of evidence indicating that ATRA can induce MDSC maturation and differentiation.
- HF1K16 is a drug encapsulated immune modulating liposome containing all-trans retinoic acid.
- A phase Ia **(NCT 05388487)** dose escalation study of HF1K16 was conducted to evaluate its tolerability, safety and to assess an immunomodulatory approach for relieving immune suppression in patients with refractory solid tumors.

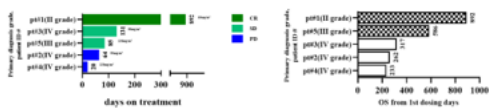
METHOD

The HF1K16 phase Ia clinical trial (NCT05388487) is being conducted to study the tolerability and safety of HF1K16 in patients with refractory solid tumors based on a **"3+3" dose escalation scheme** (45, 90, 120, 160 mg/m^2). Eligible patients had prior confirmed advanced solid tumor and failed standard treatment. HF1K16 infusions were administered in 21-day cycles (q.o.d days 1-14) and repeated until EOT. Safety and tolerability records, repeated dose PK parameters as well as exploratory PD analysis of PBMC samples are evaluated during the first cycle of treatment. Peripheral blood mononuclear cells were collected and analyzed with flow cytometry to monitor the changes in myeloid cell phenotype and T cell composition.

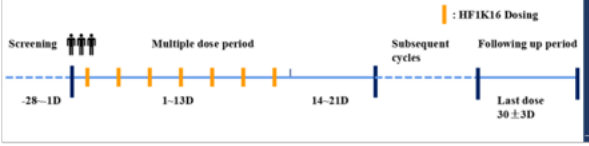
An advanced glioma-specific expansion arm

- In light of the promising preliminary efficacy results observed during the dose escalation phase, we proceeded to establish an expansion cohort in gliomas. Patient enrolled in this cohort would receive a fixed dose of either 120 mg or 180 mg depending on the patient's condition.

Observed preliminary efficacy of HF1K16 in glioma



DOSING REGIMEN



RESULTS

A total of 17 patients were enrolled in the study into dose groups of 45 mg/m^2 (n=3), 90 mg/m^2 (n=5), 120 mg/m^2 (n=4) and 160 mg/m^2 (n=4). The patients' diagnoses and prior treatments are presented in Table 1

Table 1. Patient characteristic and treatment information in dose escalation

Characteristic		
Age at enrollment, year (Median,IQR)		50.2 (50,12)
Female gender, n(%)		3 (17.6%)
ECOG performance status of 0 or 1, n(%)		17 (100%)
Primary diagnosis		17 (100%)
	Brain cancer	6 (6/17)
	Thymic epithelial cancer	1 (1/17)
	Ovarian cancer	1 (1/17)
	Stomach cancer	2 (2/17)
	Colorectal cancer	2 (2/17)
	Lung cancer	1 (1/17)
	Bile Duct Cancer	1 (1/17)
	Notochordoma	1 (1/17)
	Liver Cancer	1 (1/17)
	Carcinosarcoma	1 (1/17)
Prior therapy		
	Surgery	13 (13/17)
	Radiotherapy	10 (10/17)
	Chemotherapy	15 (15/17)
	Targeted therapy	6 (6/17)
	Immune therapy	6 (6/17)

Recurrent/refractory glioma arm

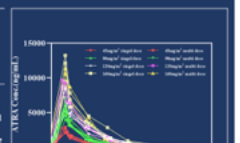
As of Sep 1th, 2024, 19 recurrent/refractory glioma patients including 9 males and 10 females had been enrolled in this study. 4 of them withdrew before finished 1st cycle. 8 had received treatment for at least 3 cycles and 1 had achieved CR after 15 cycles.

Table 2. Recurrent glioma Patient characteristic and treatment information

Characteristic		
Age at enrollment, year (Median,IQR)		44 (14)
Female gender, n(%)		9 (50%)
ECOG performance status of 0 or 1, n(%)		19 (100%)
Prior therapy		
	Grade IV (n=9)	Grade II &III (n=10)
Surgery	9	10
System Therapy	9	9
Temozolomide	9	9
Anlotinib	2	2
Bevacizumab	2	3
Tumor Treating Fields	2	0
Radiation Therapy	9	9
Sintilimab	1	0

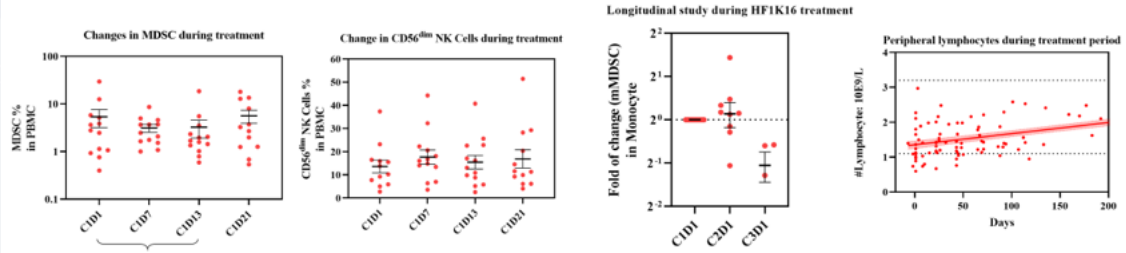
Table 3. PK profile of HF1K16 v.s. Vesanoid (oral ATRA)

	Oral 45mg/m^2 (n=5)	HF1K16 (45mg/m^2) (n=3)		HF1K16 (90mg/m^2) (n=5)	
	*SD	*SD	*MD	*SD	*MD
Tmax (h)	3	1.5	1.5	1.5	1.5
Cmax (ng/ml)	532±104	2406±438	2456±365	5717±810	5358±851
$T_{1/2}$ (h)	1.00±0.067	1.49±0.2	1.45±0.16	1.96±1.09	1.89±0.97
AUC (ng*h/ml)	1467±325	5357±671	5765±816	13854.12±1724	13174±1461
CL (ml*h/kg)	0.85±0.18	0.25±0.04	0.23±0.04	0.21±0.023	0.18±0.02
Vd(L)	166.75±34.08	33.38±7.52	32.6±6.46	30.57±5.12	32.89±5.95



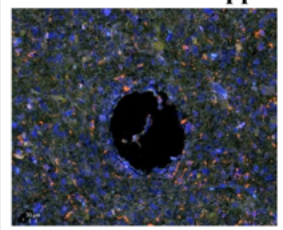
- The in vivo drug exposure was markedly elevated in the HF1K16 group relative to the oral ATRA cohort.

HF1K16 restore the immune system

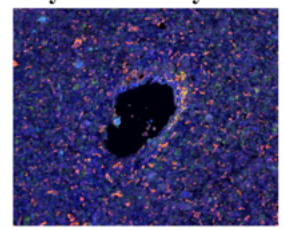


- A reduction in the number of MDSCs was noted during the dosing regimen
- Longitudinal study showed HF1K16 reduce peripheral circulating MDSCs after **3 cycles** of treatment.
- HF1K16 has been demonstrated to facilitate the restoration of peripheral lymphocytes through a multi-dosing regimen

"Window of Opportunity" IHC analysis



Tumor infiltrated myeloid cells (CD33, Yellow) and HLA-DR (Red)



Tumor infiltrated T cells (CD3, Green) and macrophage CD68 (Red)

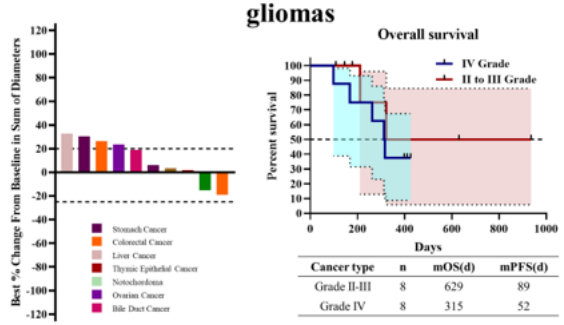
- After the completion of **5-cycle** treatment regimen of HF1K16, a recurrent **grade-4 GBM** patient proceeded with surgical intervention.
- The IHC analysis of the tumor revealed a paucity of MDSC within the tumor mass, accompanied by a notable infiltration of T cells.
- The patient has been able to maintain a satisfactory quality of life for a period exceeding **9 months** following surgical intervention, with no additional radiotherapy, chemotherapy, or other pharmacological agents, and **no evidence of recurrence**.

HF1K16 is well-tolerated in recurrent glioma patients

Table 4. **The most common treatment-related adverse events (AEs)**

	Treatment-related Adverse Events		
Event	**All grades**	**Grade 3**	**Grade 4**
Skin peeling	71.43%(10/14)	0	0
Hypercholesterolemia	64.29%(9/14)	14.29%(2/14)	0
Hypertriglyceridemia	50.00%(7/14)	14.29%(2/14)	0
Headache	50.00%(7/14)	7.14%(1/14)	0
Elevatedlow-alanine Aminotransferase	42.86%(6/14)	0	0
Vomit	42.86%(6/14)	0	0

HF1K16 demonstrated preliminary efficacy in the treatment of advanced and recurrent gliomas



Cancer type	n	mOS(d)	mPFS(d)
Grade II-III	8	629	89
Grade IV	8	315	52

- Effectiveness of HF1K16 in solid tumors (left).
- HF1K16 has the potential to be an effective treatment for brain tumors (right).

Conclusion

- HF1K16 is well tolerated at the 45 mg/m^2 ,90 mg/m^2 and 120 mg/m^{2}dose levels when given as monotherapy.
- By reprogramming MDSC and rebuilding immune homeostasis, HF1K16 has shown promising results in the treatment of recurrent glioma.
- While the interpretation of our data is limited by the small sample size, the results provide an encouraging signal and warrants further assessment. Patient recruitment continues with anticipated completion by the end of 2024.