Myeloid cell targeted immune modulation in solid tumor and brain tumor patients: an analysis of NCT05388487 phase 1 study data.

Authors: Anjie Zheng[1], Ruofan Huang[2], Yuhong Xu[3], Jinsong Wu[2] ;

[1]Academy of pharmacy, Xi'an Jiaotong-Liverpool University, Suzhou, China; [2]Department of Neurosurgery, Huashan Hospital, Fudan University, Shanghai, China, [3]HighField Biopharmaceuticals Corporation, Hang Zhou, China

BACKGROUND

- Myeloid-derived suppressor cells (MDSCs) were defined based on the myeloid cell development stage and their inhibiting function towards T cell functions. They were found to contribute to the immune suppressive environment that promote tumor growth and progression.
- 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.
- 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 phase I study comprises cohort 1-4 receiving escalating HF1K16 doses (45-160mg/m²) and cohort 5 receiving two fix doses (120mg and 180mg). HF IK16 was administered in 21-day cycles (every other day on days 1-14) until end of treatment. Patients in cohort 1-4 were monitored for changes in PBMCs during the first cycle of treatment regrading myeloid cell phenotypes and T-cel populations. Patients in cohort 5 were monitored for changes in PBMC profiling during the entire course of treatment (sample collected 1st day of each cycle). Tumor section samples from one patient in cohort 5 at three stages during tumor progression were obtained and analyzed for tumor microenvironment changes.

RESULTS

Table.1 Summary of enrolled patient data and HF1K16 treatment results

Primary diagnosis	Age	Gender	Metastasis	Prior Surgery	Targeted/Chemo-therapy	Prior Radio Therapy	Prior Immunotherapy	DOT (Cycles)	PFS (d)	OS (d)
Solid Tumor										
Thymic epithelial cancer	45	M	Liver	-	Y	Y	-	2	40	635*
Ovarian cancer	63	F	-	Y	Y	-	-	2	36	134
Stomach cancer	59	M	Lung	Y	-	-	-	2	41	146
Colorectal cancer	53	M	Liver	Y	-	-	Y	7	165	621
Lung cancer	47	M	Brain	-	Y	-	Y	2	43	255
Bile Duct Cancer	48	M	Liver	-	Y	-	-	2	42	83
Notochordoma	22	F	-	Y	-	Y	-	-	4	126
Stomach cancer	55	M	Liver	Y	Y		Y	<1	25	56
Liver Cancer	58	M	Lung	Y	Y	Y	Y	2	38	85
Colorectal cancer	46	M	Lung	Y	Y	Y	Y	1	20	74
Carcinosarcoma	49	M	-	Y	Y	Y	Y	<1	NA	174
Grade 2-3 brain tumor										
Grade 2	45	F	-	Y	Y	Y	-	>24	1030	1030*
Grade 3	54	M	-	Y	Y	Y	-	4	85	725*
Grade 3	41	F	-	Y	Y	Y	-	8	211	272*
Grade 3	35	F	-	Y	Y	Y	-	2	42	312
Grade 3	54	F	-	Y	Y	Y	-	2	32	169
Grade 2	44	M	-	Y	Y	Y	-	4	85	272
Grade 2	35	M	-	Y	Y	Y	-	9	194	210
Grade 2	54	F	-	Y	Y	Y	-	2	38	322
Grade 2	41	M	-	Y	Y	Y	-	4	94	239*
Grade 2	36	F	-	Y	Y	Y	-	2	43	202
Grade 4 brain tumor										
Grade 4	44	M	-	Y	Y	Y	-	3	64	262
Grade 4	58	M	-	Y	Y	Y	-	6	130	317
Grade 4	47	F	-	Y	Y	Y	-	4	89	519*
Grade 4	35	F	-	Y	Y	Y	-	5	113	505*
Grade 4	60	F	-	Y	Y	Y	-	2	42	492*
Grade 4	50	M	-	Y	Y	Y	-	2	42	168

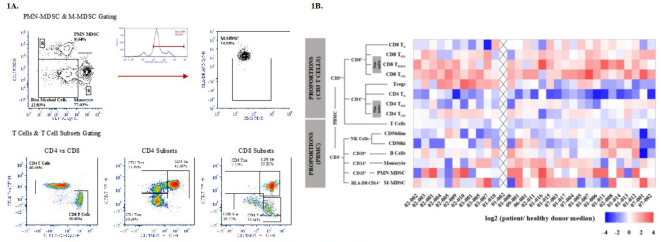


Figure.1 PBMC profiling before HF1K16 treatment

Figure.2 Changes in PBMC Myeloid cell characteristics in Patient 4 Patient 9

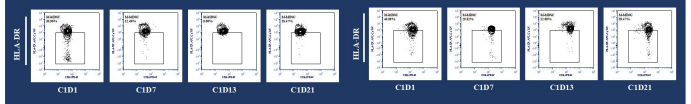
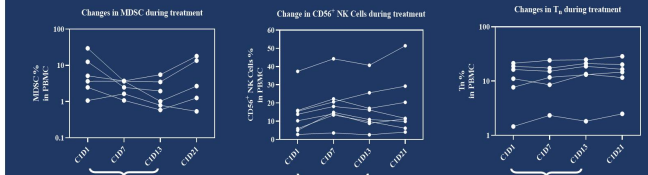


Figure.3 Changes in MDSC percentage was accompanied by increases of CD56dim NK cells and Tn levels



- Total 13 patient samples were collected during the 1st cycle of treatment. Only those with similar trends were shown.

Figure 4. Peripheral Myeloid cell profiling in Patient 12 and patient 15 during the course of treatment.

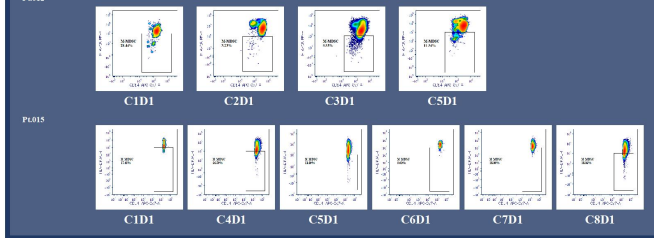
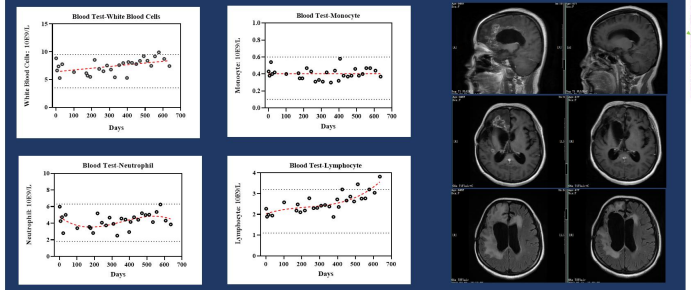


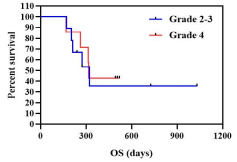
Figure.5 While Blood Cell counts during the 2year HF1K16 monotherapy treatment



- A patient with recurrent WHO grade 2 glioma achieved complete response after 10 treatment cycles. HF1K16 dosing was continued until 2 years after first enrollment. The patient has been tumor free up to date.

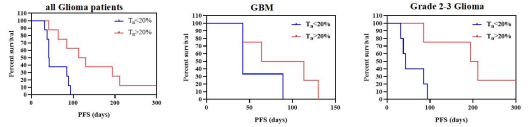
Figure 6. OS and PFS analysis in Glioma patients.

6A. OS of grade 2-3 and grade 4 patients.



Grade	Overall Survival (OS), days
2~3 (n=10)	not reached
4 (n=6)	317d

6B. PFS analysis based on Tnaive cell counts at enrollment.

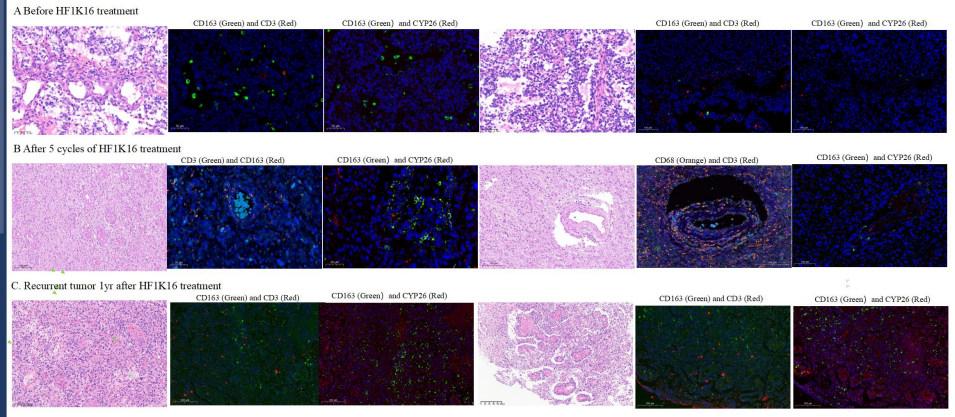


Tnaive cell levels in PBMC before HF1K16 treatment was used to divide patients into Tn high and low groups. A possible correlation with PFS was noted.

Grade	Progression Free Survival (PFS), days		Hazard Ratio	P value
	T_N>20%	T_N<20%		
2~3	202.5	43	0.13	0.02
4	88.5	42	0.28	0.23

FIgure.7 Surgically removed tumor tissue section H&E and IHC analysis before and after HF1K16 treatment

A patient with grade 4 GBM was admitted into the study upon tumor recurrence after prior surgery, radiotherapy and TMZ treatment. She received 5 cycles of HF1K16 with a best response of SD and then the lesion becomes larger. She received a second surgery to remove the tumor mass and maintain tumor free for almost a year without any medicine. However, the tumor came back again and she received the 3rd surgery for tumor removal. The samples shown were from the 1st (A), 2nd (B), and 3rd (C) surgery.



Acknowledgements & Disclosure

- We wish to thank the patients, family members and all staff that participated in the study.
- Funding of the study was provided by Hangzhou Highfield Biopharm.
- Yuhong Xu is employed and holds stocks in Hangzhou Highfield Biopharm.

References

[1] Zheng, Anjie, et al. "Sustained drug release from liposomes for the remodeling of systemic immune homeostasis and the tumor microenvironment." Frontiers in Immunology 13 (2022): 829391.
[2] Alban, Tyler J., et al. "Global immune fingerprinting in glioblastoma patient peripheral blood reveals immune-suppression signatures associated with prognosis." JCI insight 3.21 (2018).
[3] Reardon, David A., et al. "Effect of nivolumab vs bevacizumab in patients with recurrent glioblastoma: the CheckMate 143 phase 3 randomized clinical trial." JAMA oncology 6.7 (2020): 1003-1010.
[4] Tobin, R. P., Cogswell, D. T., Cates, V. M., Davis, D. M., Borgers, J. S. W., Van Gulick, R. J., Katsnelson, E., Couts, K. L., Jordan, K. R., Gao, D., Davila, E., Medina, T. M., Lewis, K. D., Gonzalez, R., McFarland, R. W., Robinson, W. A., & McCarter, M. D. (2023). Targeting MDSC Differentiation Using ATRA: A Phase I/II Clinical Trial Combining Pembrolizumab and All-Trans Retinoic Acid for Metastatic Melanoma. Clinical cancer research : an official journal of the American Association for Cancer Research, 29(7), 1209–1219. https://doi.org/10.1158/1078-0432.CCR-22-2495
[5] Rao A, Zhang X, Cillo AR, Sussman JH, Sandlesh P, Tarbay AC, Mallela AN, Cardello C, Krueger K, Xu J, Li A, Xu J, Patterson J, Akca E, Angione A, Jaman E, Kim WJ, Allen J, Venketeswaran A, Zinn PO, Parise R, Beumer J, Duensing A, Holland EC, Ferris R, Bagley SJ, Btuno TC, Vignali DAA, Agnihotri S, Amankulor NM. All-trans retinoic acid induces durable tumor immunity in IDH-mutant gliomas by rescuing transcriptional repression of the CRBP1-retinoic acid axis. bioRxiv [Preprint]. 2024 Apr 13:2024.04.09.588752. doi: 10.1101/2024.04.09.588752. PMID: 38645178; PMCID: PMC11030316.
[6] Tobin, R. P., Cogswell, D. T., Cates, V. M., Davis, D. M., Borgers, J. S. W., Van Gulick, R. J., Katsnelson, E., Couts, K. L., Jordan, K. R., Gao, D., Davila, E., Medina, T. M., Lewis, K. D., Gonzalez, R., McFarland, R. W., Robinson, W. A., & McCarter, M. D. (2023). Targeting MDSC Differentiation Using ATRA: A Phase I/II Clinical Trial Combining Pembrolizumab and All-Trans Retinoic Acid for Metastatic Melanoma. Clinical cancer research : an official journal of the American Association for Cancer Research, 29(7), 1209–1219. https://doi.org/10.1158/1078-0432.CCR-22-2495