First-in-Human Evaluation of HF50, a Novel Liposomal HER2×CD3 T Cell Engager with TLR Agonist Payload, Demonstrates Tolerability and Early Clinical Response

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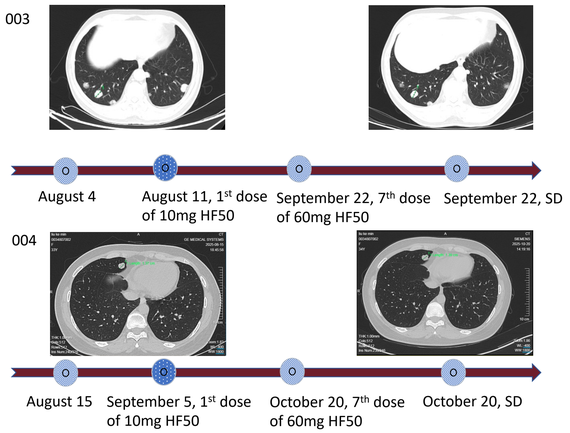
Abstract

- Background: HF50 is a novel liposomal T-cell engager (TCE) engineered to anchor both anti-CD3ε and anti-HER2 fragments on the surface for interacting with T-cell and encapsulate a TLR7/8 agonist for activating myeloid cells for complementary immune stimulation. Preclinical data suggest a wider therapeutic window and a reduced risk of cytokine release syndrome (CRS) compared to traditional TCEs. This study aims to evaluate the safety and preliminary efficacy of HF50.
- Method: This is a first-in-human, open-label, Phase I dose-escalation study (NCT06822998) designed to evaluate the safety, tolerability, pharmacokinetics, and preliminary anti-tumor efficacy of HF50. The trial enrolls patients with advanced HER2-positive or HER2-low (IHC ≥ 1+) solid tumors who have failed, are intolerant to, or lack effective standard treatment options. We utilize a weekly intravenous infusion schedule that incorporates a step-up dosing regimen to mitigate potential CRS.

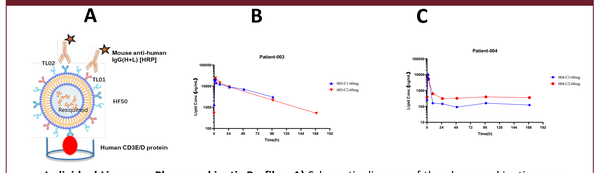
Subject Demographics, AEs and Responses

Subject	Sex	Age	Pathology	Her-2	Drug-Related AEs (Definite, Probable, Possible)	Treatment Response per RECIST 1.1		
						W7	W13	W19
001	M	52	Salivary duct carcinoma	IHC 2+, FISH(-)	Grade 1 discomfort in the cervical lymph node region	SD	PR	PR
002	M	59	Salivary duct carcinoma	IHC 2+, FISH(-)	Grade 1 blister at the tumor site and persistent site discharge	PD	-	-
003	M	54	Salivary duct carcinoma	IHC 3+	Grade 1 CRS (fever)	SD	-	-
004	F	34	Adenoid cystic carcinoma	IHC 1+	Grade 1 rash	SD	-	-

Radiological Evaluation in Subject 003 & 004



Detection of HF50 Particles in the Patients' Plasma After Injection

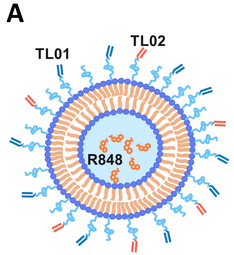


Individual Liposome Pharmacokinetic Profiles. A) Schematic diagram of the pharmacokinetic assay methodology. Plasma concentrations of liposome following the 2nd dose (Cycle 1, Day8) and 4th to 6th dose (Cycle 2, D1 or 8 or 15) in patients from the 60 mg cohort (**B**: Patient-003; **C**: Patient-004).

Co-Culture After Ex Vivo Stimulation of Patient T Cells

A) Schematic of the ex vivo T cell co-culture experimental workflow. **B)** Longitudinal analysis of Perforin levels in co-culture supernatants. **C)** Longitudinal analysis of normalized IFN-γ (Interferon-gamma) levels in co-culture supernatants.

HF50 Design

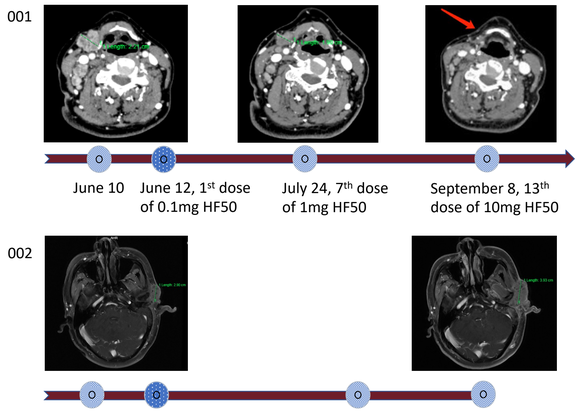


A) Liposomal TCE HF50 with an Anti-CD3ε (TL02) and anti-HER2 (TL01) fragments on surface, and TLR7/8 agonist payload inside for myeloid cell activation. **B)** HF50 dose levels and corresponding component doses.

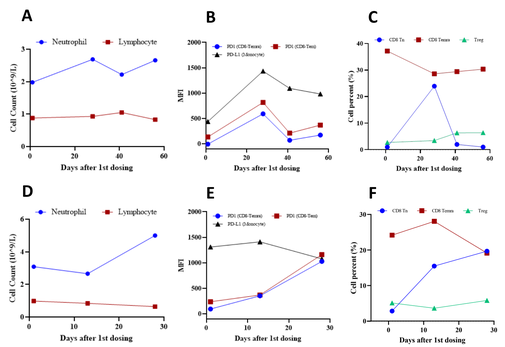
B

HF50 Dose/mg	Liposome Particles Dose/particles×10^{11}	TL02 Dose/mg	R848 Dose/mg
0.1	7.14	0.0007	0.004
1	71.43	0.007	0.04
10	714.32	0.07	0.4
60	4285.93	0.42	2.4

Radiological Evaluation in Subject 001 & 002



Analysis of Patients' PBMCs During the Course of HF50 Treatment



Dynamic changes in immune cell populations are shown for **Patient 003 (Top Row, A-C)** and **Patient 004 (Bottom Row, D-F)** during the course of HF50 treatment.
- **(A, D)** Absolute counts of peripheral neutrophils and lymphocytes over time.
- **(B, E)** Expression levels (MFI) of PD-1 on CD8+ T cell subsets (Temra and Tem) and PD-L1 on Monocytes.
- **(C, F)** Percentages of T cell subsets, including CD8+ Naive T cells (Tn), CD8+ Effector Memory T cells (Temra), and Regulatory T cells (Treg).

Conclusion

HF-50 demonstrated a manageable safety profile and was well-tolerated at the tested dose levels in this cohort. T cell activation and inflammatory responses were observed at all dose levels, leading to preliminary anti-tumor activity in some patients. These findings support continued dose escalation and further investigation of HF-50 in this population.

Acknowledgments

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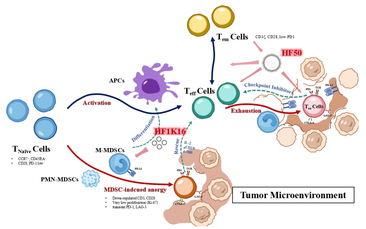

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