Phase I Trial of Intratumoral Therapy Using HF10, an Oncolytic HSV-1, Demonstrates Safety and Efficacy in HSV+/HSV- Patients with Refractory and Superficial Cancers

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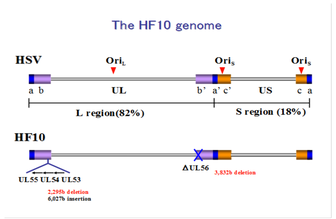
Introduction

HF10 is a replication-competent spontaneously occurring mutant of the HF strain of Herpes Simplex Virus type 1 (HSV-1). TAKARA BIO INC. is developing HF10 for use as an oncolytic virotherapy to treat head and neck cancer and solid tumors with cutaneous and/or superficial lesions, including squamous cell carcinoma of the skin, carcinoma of the breast, and malignant melanoma. HF10 is administered by intratumoral injection.

Following infection of human cells with HSV-1, the virus replicates and destroys infected cells. HF10 differs from wild type strains of HSV-1, because although replication-competent, it has a number of deletions and insertions in its genome, resulting in the lack of functional expression of UL43, UL49.5, UL55, and UL56 (Figure 1). A 3832 base pairs (bp) deletion in the right end of the UL and UL/IRL junction of the HF10 genome, resulting in loss of expression of the UL56 gene, appears to result in the attenuated neuroinvasiveness and neurovirulence of HF10 observed in animal studies.



Shown are the 3832 bp deletion at the UL and UL/IRL junction and 2295 bp deletion and rearrangement at the left end of the HF10 genome.

Figure 1: Comparison of HF10 and Wild Type HSV-1 Genomes

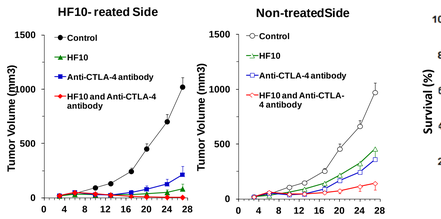


Figure 2: Tumor volume on HF10-treated side (A) and non-treated side (B)

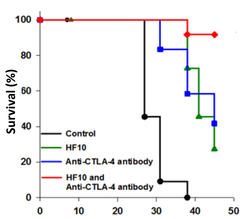


Figure 3: Survival Benefit

HF10 has been evaluated in combination with an anti-cytotoxic T lymphocyte antigen 4 antibody (anti-CTLA-4 antibody), and the combination was found to be improved anti-tumor effects not only in the HF10-treated side (Figure 2A) but also in the non-treated side (Figure 2B) and survival (Figure 3) in mice that have been inoculated with CT26/NY-ESO1 cells.

This study suggests that the combination treatment elicits enhanced tumor immunity, and might confer a clinical benefit in patients treated with the combination. A phase II study combining HF10 with ipilimumab is currently being initiated.

Study Design

Study Objectives
- Evaluate the safety and tolerability of HF10 in patients with refractory head and neck cancer and other solid tumors with cutaneous and/or superficial lesions
- Characterize viral replication after treatment with HF10
- Evaluate evidence of overall and local antitumor activity after single and repeat injections of HF10

Study Design
- Dose escalation of multiple doses of HF10, administered as single and repeat intratumoral injections
- "3+3" design, starting dose of 1.0mL $1x10^5$ $TCID_{50}$ HF10

Study Treatment
- Intratumoral injection of HF10 into single target lesion

Key Inclusion Criteria
- Histologically-confirmed solid tumors that have progressed on standard therapies
- Measurable (RECIST 1.0) superficial tumor
- Adequate hepatic, renal, bone marrow function
- ECOG 0, 1, 2
- Life expectancy > 12 weeks
- No preexisting neurologic abnormalities (CTCAE 3.0)

Evaluations
- Response: RECIST 1.0; 4-week intervals
- Safety: Adverse events, vital signs, ECG, clinical laboratory tests, physical exams
- Viral Shedding: qPCR of blood, saliva, urine

Results

Table 1: Summary of Cohorts

Study Enrollment		
Single Injection	Cohort 1 ($1x10^5$ $TCID_{50}$)	N=5
	Cohort 2 ($3x10^5$ $TCID_{50}$)	N=4
	Cohort 3 ($1x10^6$ $TCID_{50}$)	N=4
	Cohort 4 ($1x10^7$ $TCID_{50}$)	N=4
Repeat Injection	Cohort 1 ($1x10^6$ $TCID_{50}$)	N=3
	Cohort 2 ($1x10^7$ $TCID_{50}$)	N=5
	Expansion ($1x10^7$ $TCID_{50}$)	N=3

Total Accrual: 28 Patients

Table 2: Patient Demographics

Characteristics	N(%)
Age (Years)	
Median	71
Range	35-92
Sex	
Male	14 (50%)
Female	14 (50%)
ECOG Status	
0	12 (42.9%)
1	15 (53.6%)
2	1 (3.6%)
HSV-1 antibody	
(+)	24 (86%)
(-)	4 (14%)

Table 3: Number of Patients with AEs

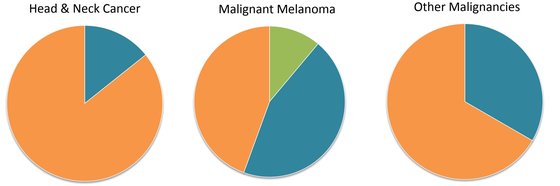
Number of Patients with Adverse Events	N(%)
Safety evaluable patients	24 (100%)
With Any Adverse Event	21 (87.5%)
With Possibly, Probably, Or Definitely HF10 Related Adverse Events	8 (33.3%)
With Severity Grade 3, 4 or 5*	5 (20.8%)
With Any Serious Adverse Events*	5 (20.8%)
Who Died Due to Adverse Events*	3 (12.5%)

*unrelated to HF10

Table 4: TEAEs occurring in > 1 Patient

Treatment-Emergent Adverse Events	N(%)
Number of patients with TEAEs	21 (87.5%)
Chills	3 (12.5%)
Fatigue	3 (12.5%)
Localized Edema	2 (8.3%)
Nausea	3 (12.5%)
Constipation	2 (8.3%)
Diarrhea	2 (8.3%)
Hypokalemia	2 (8.3%)
Weight Decreased	3 (12.5%)
Hemoglobin Decreased	2 (8.3%)
Pruritus	2 (8.3%)
Urinary Tract Infection	2 (8.3%)
Anxiety	2 (8.3%)

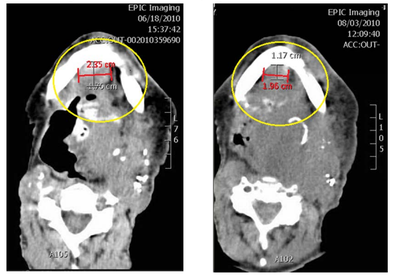
Figure 4: Target Lesion Response by Disease Type Assessed After Completion of HF10 Therapy



Head & Neck Cancer: N=14 SD: 2 (14%) PD: 12 (86%)
Malignant Melanoma: N=9 SD: 4 (44%) PD: 4 (44%) PR: 1 (11%)
Other Malignancies: N=3 SD: 1 (33%) PD: 2 (66%)

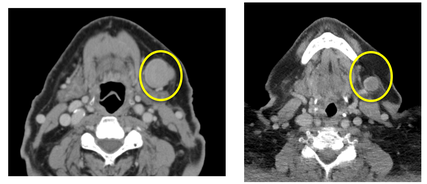
Response measured in target lesions according to RECIST 1.0 , four weeks after the completion of treatment.

Figure 5: Target Lesion Regression, Squamous Cell Carcinoma, Patient 0002



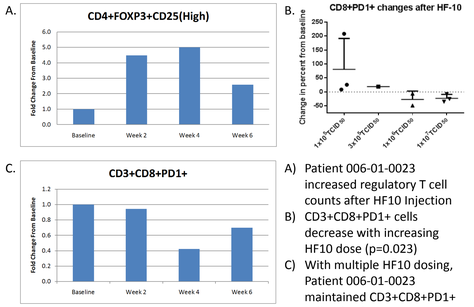
Left: Lesion Pre-HF10 Injection (Day 1 baseline)
Right: Lesion Post-HF10 Injection (Day 57)
Lesion: Squamous Cell Carcinoma, anterior floor of mouth (Patient 001-01-0002)

Figure 6: Target Lesion Response, Malignant Melanoma, Patient 0020



Left: Lesion Pre-HF10 Injection (Day 1 baseline) 28x27mm
Right: Lesion 9 months after final injection LD: 19x19mm
Lesion: Malignant Melanoma, Left Neck Lymph Node (Patient 006-01-0020), demonstrating XX% decrease

Figure 7: Correlative Data



A) Patient 006-01-0023 increased regulatory T cell counts after HF10 Injection
B) CD3+CD8+PD1+ cells decrease with increasing HF10 dose (p=0.023)
C) With multiple HF10 dosing, Patient 006-01-0023 maintained CD3+CD8+PD1+ cell reductions

Conclusions

Treatment with HF10 has been observed to be well tolerated with a low frequency of adverse effects. Adverse effects that were observed were mild in severity and did not lead to treatment discontinuation. Adverse effects were consistent with those observed in patients treated with other oncolytic viruses. There were no significant differences observed in HSV-1+ or HSV-1- patients.

Viral shedding was observed infrequently, and resolved without the requirement of antiviral treatment. Evaluating the response of target lesions, 1 partial response (4%) was observed and 7 stable disease (27%) was observed of 26 treated patients. However when target lesion response was stratified for disease type, it was observed that melanoma patients demonstrated a greater frequency of SD+PR than patients with head & neck cancer or other superficial malignancies (56% vs 14% vs 33% respectively).

In addition, HF10 appears to modulate checkpoint receptor expression on T cells, including regulatory T cells (Treg) which often express CTLA-4, supporting design of the phase II trial combining HF10 with anti-CTLA4 depletion of suppressive Treg cells to enhance antitumor immunity

Ongoing Development

As a result of the favorable safety and treatment profile observed in this phase I study, as well as the preclinical observed potential of the combination of HF10 with anti-CTLA-4 antibody, a phase II study in patients with unresected and/or metastatic melanoma is currently being initiated.

Ipilimumab-naive patients will be treated with 4 doses of Ipilimumab in combination with up to 19 injections of HF10 at a dose of $1x10^7TCID_{50}$. The first patient is expected to be enrolled in July 2014.