Delayed Tumor Response and Safety Profile in Patients with Refractory Superficial Cancers Treated with Intratumoral Injections of HF10, an Oncolytic HSV-1

Robert H.I. Andtbacka[1], Kenneth F. Grossmann[1], Hung T. Khong[1], Maki Tanaka[2], Richard S. Ungerleider[3], Aislyn Boran[3], and Robert L. Ferris[4]

[1] Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; [2]Takara Bio, Inc., Shiga, Japan; [3]Theradex, Princeton, NJ; [4]University of Pittsburgh Cancer Institute, Pittsburgh, PA

Introduction

Takara Bio Inc. is developing HF10 as an oncolytic viral therapy for intratumoral injection into cutaneous and/or superficial lesions. HF10 is a spontaneously occurring mutant of the HF strain of Herpes Simplex Virus type 1 (HSV-1). HF10 is clearly different from other attenuated HSV and wild type strains; in preclinical models it was shown to be replication-competent, lack neuro-invasiveness and have attenuated virulence.

Following infection of human cells with HSV-1, the virus replicates and destroys infected cells. HF10 has been evaluated in mouse bilateral xenograft models using M-3 melanoma cells. One of 2 tumors was injected with HF10. The treatment was found to have improved anti-tumor effects not only in the HF10-treated side but also in the non-treated side, suggesting a systemic effect. Survival was also improved in mice that have been inoculated with M-3 melanoma cells.

The primary purpose of this Phase I study was to assess the safety and tolerability of HF10 in patients with solid, superficial tumors.

Study Design

Study Objectives

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

Study Design

- Stage 1: Dose escalation of a single HF10 administration at doses of: 1x 10^5, 3 x 10^5, 1 x 10^6, and 1 x 10^7 TCID50 using a "3+3" design
- Stage 2: Repeated administrations of HF10 (up to 4) at doses of 1 x 10^6, and 1 x 10^7 TCID50

Evaluations

- Safety: Adverse events by CTCAE ver. 3.0
- Response: RECIST 1.0; 4-week intervals
- Viral Shedding: qPCR of blood, saliva, urine

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)

Study Treatment

- Intratumoral injection of HF10 into a single target tumor more than 2 cm away from major vascular structures using direct visualization or endoscopy, as clinically determined. Ultrasound or computed tomography (CT) guidance may be used if necessary.

Patient Demographics and Disposition

Table 1: Patient Demographics

Characteristics	N(%)	Characteristics	N(%)
Age (Years)		Sex	
Median	70.5	Male	13 (50%)
Range	35-92	Female	13 (50%)
ECOG Status		HSV-1 antibody	
0	12 (46.2%)	(+)	23 (88%)
1	13 (50.0%)	(-)	3 (12%)
2	1 (3.8%)		

Table 2: Summary of Cohorts

Study Enrollment (26 safety evaluable patients)		
Single Injection	Cohort 1 (1x10^5 $TCID_{50}$)	N=5
	Cohort 2 (3x10^5 $TCID_{50}$)	N=3
	Cohort 3 (1x10^6 $TCID_{50}$)	N=4
	Cohort 4 (1x10^7 $TCID_{50}$)	N=3
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

Results

Table 3: Safety Summary

Treatment-Emergent Adverse Events (TEAEs)	Number of patients
Safety evaluable	26
With any TEAEs	24 (92.3%)
With possible, probable, or definite drug-related TEAEs	9 (34.6%)
With severity Gr 3, 4 or 5 for drug-related TEAEs	0 (0%)
With any serious, drug-related TEAEs	0 (0%)
Who discontinued drug due to drug-related TEAEs	0 (0%)

Table 4: Safety Profile

Drug Related TEAEs	N(%)
Safety evaluable patients	26
Number of patients with TEAEs	9 (34.6%)
Chills	3 (11.5%)
Fatigue	2 (7.7%)
Injection Site reaction	6 (23.1%)
Malaise	1 (3.8%)
Pyrexia	1 (3.8%)
Haematoma	1 (3.8%)
Hypotension	1 (3.8%)
Nausea	1 (3.8%)
Dehydration	1 (3.8%)
Genital swelling	1 (3.8%)
Scrotal ulcer	1 (3.8%)
Pruritus	1 (3.8%)

Table 5: Response Summary

Best Overall Response Rate (Total 24 patients)	N (%)
Malignant Melanoma Patients:	9 (37.5%)
Overall response (CR +PR)	0
Stable Disease (SD)	**6 (66.7%)**
Progressive Disease (PD)	3 (33.3%)
Not Evaluable (NE)	0
Head & Neck Cancer/Other Malignancies Patients:	15 (62.5%)
Overall response (CR +PR)	0
Stable Disease (SD)	**2 (13.3%)**
Progressive Disease (PD)	9 (66.7%)
Not Evaluable (NE)	4 (20.0%)

Case #1: Malignant Melanoma Patient 0020

Patient 0020: Stage 2, 1 x 10^6 TCID50/mL dose cohort

82 y/o male with metastatic melanoma of left frontal scalp

Prior therapies: Intralesional Interleukin 2 + intralesional Ipilimumab

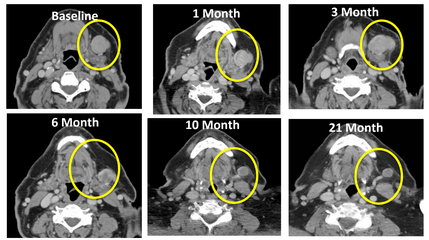
Completed study per protocol (4 HF10 injections in left submandibular lymph node)

HF10-related TEAEs experienced: None

Best local response: PD Best overall response: SD

Lesion #	*Baseline (mm)*	*1 mo. (mm)*	*3 mo. (mm) Off-Study*	*6 mo. (mm)*	*10 mo. (mm)*	*21 mo. (mm)*
1 injected	28	*29*	*39*	*25*	*19*	*16*
2 R scalp	15	*10*	*0*	*0*	*0*	*0*
3 R forehead	15	*0*	*0*	*0*	*0*	*0*
6 C forehead	15	*0*	*0*	*0*	*0*	*0*

Figure 1: Patient 0020 Target Lesion Response



Case #2: Malignant Melanoma Patient 0027

Patient 0027: Stage 2, 1 x 10^7 TCID50/mL dose cohort

60 y/o male with melanoma of left forehead

Prior therapies: Temodar, intralesional Oncovex (T-VEC), Ipilimumab

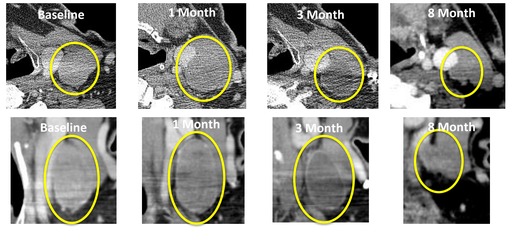
Completed study per protocol (4 HF10 injections in left neck Level 3 lymph node)

HF10-related TEAEs experienced: Gr1 fatigue, Gr 1 inj. site haematoma

Best local response: SD Best overall response: SD

Lesion #	*Baseline (mm)*	*1 mo. (mm)*	*3 mo. (mm) Off-Study*	*8 mo. (mm)*
1 injected	41	*52*	*39*	*16*
2 lung	14	*14*	*12*	*13*
3 lung	49	*45*	*41*	*37*

Figure 2: Patient 0027 Target Lesion Response



Discussion/Conclusions

In this Phase I study, treatment with HF10 was well-tolerated with no grade 3 or greater drug-related treatment emergent adverse events. Drug-related Grade 1 or 2 adverse events, which were low in frequency (34.6%), did not lead to treatment discontinuation, and were consistent with those observed in patients treated with other oncolytic viruses. There were no significant differences in adverse events between HSV-1 seropositive and seronegative patients. Viral shedding was observed infrequently, and resolved without the requirement of antiviral treatment.

In 24 patients evaluable for response, 8 (33%) had stable disease (SD). When target lesion response was stratified for disease type, it was observed that melanoma patients (N=9) demonstrated a greater frequency of SD than patients with head & neck cancer and other superficial malignancies (N=15) (66.7% vs 13.3%, respectively). Responses for 2 patient cases presented herein suggest that HF10 has both local and systemic antitumor activity, given that non-HF10-injected tumors showed stability or decrease in size. For patient 0020, 3 uninjected lesions completely regressed just 3 months after initiating treatment.

The maximum number of injection given was 4 and it is likely that this may not be sufficient to demonstrate a robust response in injected and uninjected lesions. However, even with only 4 injections of HF10, the 3 cases presented herein indicate that HF10 may have delayed responses:

- *Patient 0020*: The HF10 injected left submandibular lymph node reduced in size by 30% at 8 months and 41% by 21 months after treatment initiation. After 29 months the patient remains disease-free and the submandibular lymph node is normal in size.
- *Patient 0027*: The HF10 injected left neck level 3 lymph node reduced in size by 61% at 8 months after treatment initiation
- *Patient 0019*: The HF10 injected left lateral thigh lesion did not reduce in size. However, 4 months after treatment the patient underwent a surgical resection of the lesion showing no evidence of melanoma. Hence the patient had a pathological complete response. The patient remains disease-free for over 2 years.

Ongoing Development

As a result of the favorable safety and treatment profile observed in this phase Ib 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 underway (ClinicalTrials.gov Identifier: NCT02272855). Ipilimumab-naive patients will be treated with 4 doses of ipilimumab in combination with up to 19 injections of HF10 at a dose of 1x$10^7$$TCID_{50}$/mL. The first patient was treated in November 2014.

Case #3: Patient 0019 Malignant Melanoma

Patient 0019: Stage 2, 1 x 10^6 TCID50/mL dose cohort]

37 y/o female with melanoma of left lateral thigh

Prior therapies: adjuvant PEG interferon

Completed study per protocol (4 HF10 injections in distal lateral left thigh)

HF10-related TEAEs experienced: Gr1 malaise, Gr 1 inj. site soreness, Gr1 pruritus

Best local response: PD Best overall response: PD

Lesion #	*Baseline (mm)*	*1 mo. (mm)*	*3 mo. (mm) Off-Study*	*4 mo.*	*21 mo.*
1: injected	13	*11*	*17*	*Radical resection – no residual tumor (pathological CR)*	*No evidence of disease*

Figure 3: Patient 0019 Target Lesion Response