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# A PHASE I TRIAL OF INTRATUMORAL ADMINISTRATION OF HF10 IN PATIENTS WITH REFRACTORY SUPERFICIAL CANCER: IMMUNE CORRELATES OF VIRUS INJECTION

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## BACKGROUND

- HF10 is a naturally mutated strain of herpes simplex virus *I* (*HSV*-1)
- HF10 is replication-competent and exhibits attenuated neuro-invasiveness due to several genomic deletions and insertions
- *In vivo* oncolytic activity has been demonstrated in various solid tumor models.
- HF10 has also demonstrated systemic anti-tumor activity via activation of tumor-immunity.
- HF10 intratumoral treatment has been well-tolerated in human studies conducted in Japan

## STUDY OBJECTIVES

- Assess safety and determine recommended dose for further studies
- Characterize change in HF10 viral replication in body fluids
- Assess anti-tumor activity and intratumoral viral replication
- Evaluate antitumor lymphocyte response and identify serum biomarkers of antitumor activity

## STUDY DESIGN

- Open-label, multi-center dose escalation study evaluating both single and repeat intratumoral dosing with HF10 injection
- Study has a "3 + 3" design with a 4-dose escalation scheme
- Starting dose of HF10 in Stage I is 1 x $10^5$ $TCID_{50}$/dose with incremental dose escalations of 3 x $10^5$ $TCID_{50}$/dose, 1 x $10^6$ $TCID_{50}$/dose and 1 x $10^7$ $TCID_{50}$/dose
- Stage II is evaluating multiple dosing at 1 x $10^6$ $TCID_{50}$/dose and 1 x $10^7$ $TCID_{50}$/dose (Figure 1)

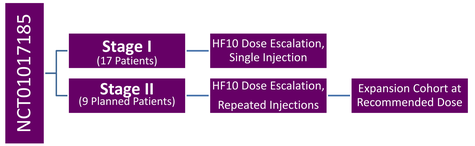



**Figure 1: Treatment Arms**

## METHODS

**Key Inclusion Criteria**
- Histologically-confirmed solid tumors that have failed standard therapies
- Tumor is accessible for injection and measurement
- ECOG performance status of 0, 1, or 2

**Key Exclusion Criteria**
- Bleeding diathesis
- Target tumor within 2cm of major vessels

## EVALUATION CRITERIA

**Safety**
- Adverse events, vital signs, ECG, laboratories, physical exam

**Viral Detection**
- PCR for HF10 in blood, saliva, urine Days 1-5, 8, 15, 22 after each injection

**Efficacy**
- RECIST 1.0 for overall tumor response, modified RECIST 1.0 for evaluation of target tumor response

**Correlative Research**
- Optional tumor biopsies in Stage I, mandatory in Stage II
- Blood collection at baseline and 2 weeks post each injection

## RESULTS

- A total of 21 patients have been enrolled to date, of which 19 patients with various tumor types have been treated (Table 1):

**Stage I**

Cohort 1 (1 x $10^5$ $TCID_{50}$), n= 5 Cohort 3 (1 x $10^6$ $TCID_{50}$), n= 4

Cohort 2 (3 x $10^5$ $TCID_{50}$), n= 4 Cohort 4 (1 x $10^7$ $TCID_{50}$), n= 3

**Stage II**

Cohort 1 (1 x $10^6$ $TCID_{50}$), n= 3 Cohort 2 (1 x $10^7$ $TCID_{50}$), n=1

- Of 16 efficacy evaluable patients, 9 achieved stable disease (Table 2), (Figure 2)
- 13 have experienced treatment-emergent adverse events (Table 3)
- No dose limiting toxicities nor any Serious Adverse Events related to HF10 therapy were observed
- One HSV-1 seronegative patient has been treated in Stage II

**Table 1: Tumor Types**

| Tumor Type | N (Efficacy Evaluable) | N (%) |
|---|---|---|
| Stage 1 | 15 | |
| Head & Neck | | 9 (60%) |
| Melanoma | | 4 (27%) |
| Sarcoma | | 1 (6%) |
| Colorectal | | 1 (6%) |
| Stage 2 | 4 | |
| Melanoma | | 2 (50%) |
| Head & Neck | | 2 (50%) |

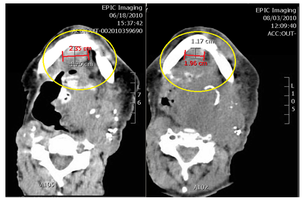
**Table 2: Tumor Response**

| Response | N (Efficacy Evaluable) | N (%) |
|---|---|---|
| Stage 1 | 13 | |
| Progressive Disease | | 7 (54%) |
| Stable Disease | | 6 (46%) |
| Stage 2 | 3 | |
| Progressive Disease | | 0 (0%) |
| Stable Disease | | 3 (100%) |

**Table 3: Treatment-Emergent Adverse Events Reported by ≥2 Patients**

| Treatment Emergent Adverse Event (TEAE) | N (%) |
|---|---|
| Safety Evaluable Patients | 15 |
| Number of Patients with TEAEs | 13 (86.7%) |
| Chills | 2 (13.3%) |
| Fatigue | 2 (13.3%) |
| Constipation | 2 (13.3%) |
| Nausea | 2 (13.3%) |
| Tongue edema | 2 (13.3%) |
| Haemoglobin decreased | 2 (13.3%) |
| Weight decreased | 2 (13.3%) |
| Hypokalemia | 2 (13.3%) |
| Anxiety | 2 (13.3%) |

**Figure 2: SCCHN Lesion Pre- and Post-HF10 Injection (Anterior Floor of Mouth, Patient 001-01-0002.)**




Left: Lesion Pre-HF10 Injection (Baseline) Right: Lesion Post-HF10 Injection (Day 43)

- Patient demonstrated a 20% decrease in the longest diameter of the injected lesion

## CORRELATIVE STUDY METHODS

- Peripheral blood from 13 patients treated in Stage I drawn at baseline prior to HF10 administration and post-injection Day 15
- Multicolor flow cytometry performed on patient lymphocytes using antibodies for CD3, CD4, CD8, CCR7, CD45RA, TIM3, PD1, CTLA-4, CD56, CD25, CD11c, CD14, TGF-beta (LAP), and Foxp3, as well as fixable viability dye (ebioscience) to exclude dead cells
- Luminex 30-plex assay performed on patient serum according to manufacturer's specifications
- Statistical analysis of Luminex data (Wilcoxon Signed Rank test) and flow cytometry data (student's t-test) performed using GraphPad Prism software

## CORRELATIVE STUDY RESULTS

**Peripheral blood lymphocytes**
- CD8+PD1+ population serially decreased with increasing HF10 dose; changes were significant when the two highest and lowest dose groups were pooled and compared (p=0.023) (Figure 3A)
- CD14+CD11c+ population increased with increasing HF10 dose (p=0.063) (Figure 3B)

**Peripheral blood cytokine profile**
- 29 of 30 cytokines analyzed via Luminex found to have no significant changes with HF10 injection therapy (Table 4)
- IL-8 increased in all patients post-injection (p=0.0078) (Figure 4)

**Patients 10 and 11 had large increases in CD14+CD11c+ population with a concurrent increase in IL-8.**

**Figure 3: Dose Response of CD8+PD1+ (A) and CD14+CD11c+ (B) Peripheral Blood Lymphocyte Populations Pre- and 15 Day Post-HF10 Injection**

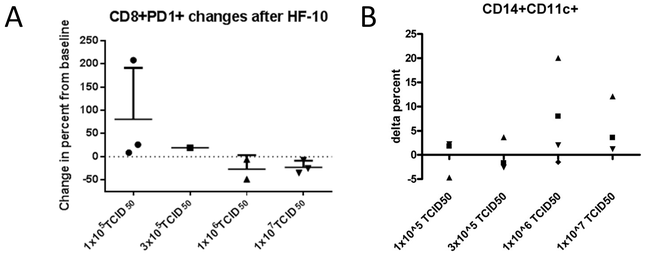
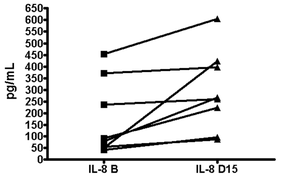



**Table 4: Luminex Analyte Summary**

| Luminex Analyte | Average Pre Treatment pg/mL | Average Post Treatment pg/mL | P-value |
|---|---|---|---|
| IL-1B | 201 | 244 | NS |
| IL-2 | 2023 | 3604 | NS |
| IL-4 | 4960 | 4191 | NS |
| IL-5 | 355 | 250 | NS |
| IL-6 | 521 | 476 | NS |
| IL-7 | 461 | 564 | NS |
| IL-8 | 173 | 295 | *0.0078 |
| IFN-α | 1375 | 1149 | NS |
| GM-CSF | ND | ND | NS |
| IFN-γ | ND | ND | NS |
| TNF-α | 127 | 106 | NS |
| IL-12 p40/p70 | 1096 | 1083 | NS |
| IL-13 | 488 | 426 | NS |
| IL-15 | 1174 | 1077 | NS |
| IL-17 | 79 | ND | NS |
| MCP-1 | 1677 | 1766 | NS |
| MIP-1a | 5302 | 2665 | NS |
| MIP-1b | 126 | 131 | NS |
| Eotaxin | 164 | 189 | NS |
| Rantes | 4527 | 5134 | NS |
| IP-10 | 47 | 51 | NS |
| MIG | 214 | 229 | NS |
| IL-2R | 853 | 831 | NS |
| IL-1RA | 380 | 408 | NS |
| EGF | 152 | 108 | NS |
| FGF-b | 129 | 72 | NS |
| G-CSF | 142 | 140 | NS |
| HGF | 657 | 840 | NS |
| VEGF | 7 | 5 | NS |
| IL-10 | ND | ND | NS |

**Figure 4: IL-8 Concentration in Peripheral Blood Pre- and 15 Day Post-HF10 Injection**




## CONCLUSIONS

- Treatment with intratumorally-injected HF10 has been well tolerated in multiple types of solid tumor malignancies and in patients who are both naïve or who have had previous exposure to HSV-1
- There appears to be generalized IL-8 related inflammatory response to treatment along with increased peripheral blood monocytes. Patients 10 and 11 responded strongly along both of these axes, though this did not correlate with clinical response.
- Decreased CD8+PD1+ cells may indicate a shift towards a non-exhausted functional CTL phenotype, or homing of outbound PD1+ cells to the injected tumor
- Future work with tissue correlative studies using post-injection specimens are underway