HFD2 (Carnapetureve, C-REV) is a biologically efficacious replication-competent oncolytic virus derived from HSV-1. In preclinical settings, combining a mouse anti-CTLA-4 antibody with C-REV has shown a higher rate of complete tumor regression and significant improvement in the median overall survival compared to either monotherapy. The Phase II trial of C-REV and ipilimumab (anti-CTLA-4 antibody) combination treatment was designed to assess the efficacy and safety of patients with Stage IB-II, III, or IV metastatic malignant melanomas.

**Methods**

- **Study Design:**
  - Phase II, open-label, randomized, 2:1, single-arm study to evaluate the safety and efficacy of the combination therapy of C-REV and ipilimumab.
  - Eligible patients: Stage IB-II, III, or IV metastatic malignant melanoma.
  - Treatment regimen: C-REV at 1x10⁷ TCID₅₀/mL IT and Ipilimumab 3mg/kg IV.
  - Study duration: 24 weeks.
  - End of study: Includes those patients who went off treatment.

- **Patients Characteristics:**
  - Total (N=46):
    - 34 (73.9%) free survival
    - 12 (26.1%) disease progression
  - Stage IIIB (n=20), IIIC (n=43), IV (n=37)
  - Prior Chemotherapies:
    - 8 (18.2%)
    - 17 (37.0%)
    - 34 (73.9%)
  - Disease stage:
    - 20% IIIB, 43% IIIC, 37% IV

- **Response of Patient 001-040:**
  - Injection Right Axilla Metastatic Lymph Node
  - Non-Injected Liver Segment 4A
  - Measured lesion disappearance in 23% and 2% of patients.

- **Efficacy and Genetic Analysis for a Phase II Multicenter Trial of HF10 (Merrick M., Nishiyama R., Hung T. Khong R.):**
  - Treatment with C-REV plus ipilimumab was well tolerated. Of 44 pts enrolled and treated, 6 (13.6%) had disease stabilization, 17 (38.6%) had partial response, 17 (38.6%) had complete response, and 4 (8.7%) were confirmed responders.
  - 44 pts: 26 (59.1%) were treatment naïve and 18 (40.9%) with ≥ 1 prior cancer therapy for melanoma.
  - 44 pts: 7 (15.9%) were metastatic to liver, 20 (45.5%) to lymph nodes, 15 (34.1%) to lung, 12 (27.3%) to brain, and 8 (18.2%) to bone.
  - 44 pts: 57% were treatment naïve and 43% with ≥ 1 prior cancer therapy for melanoma.

**Discussion/Conclusions:**

- **Treatment with C-REV plus ipilimumab was well tolerated.** Of 44 pts enrolled and treated, 6 (13.6%) had disease stabilization, 17 (38.6%) had partial response, 17 (38.6%) had complete response, and 4 (8.7%) were confirmed responders.
- **Conclusion:** The combination C-REV and ipilimumab treatment demonstrated a favorable benefit/risk profile and encouraging antitumor activity in advanced melanoma pts by inducing immune cell infiltration in the tumor microenvironment.