Efficacy and Genetic Analysis for a Phase II Multicenter Trial of HF10 (Canerpaturev), a Replication-competent HSV-1 Oncolytic Immunotherapy and Ipilimumab Combination Treatment in Patients with Stage IIIB-IV Unresectable or Metastatic Melanoma

Abstract # 9541

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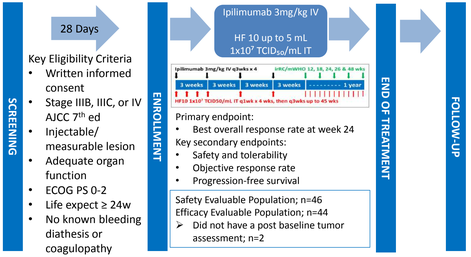
Introduction

HF10 (Canerpaturev; C-REV) is a bioselected replication-competent oncolytic virus derived from HSV-1. In preclinical studies, combining a mouse anti-CTLA-4 antibody with C-REV has shown a higher rate of complete tumor disappearance 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 IIIB, IIIC, or IV metastatic malignant melanoma.

Methods

Study Design



Results

Patients Characteristics

	Total (N=46)
Sex -n(%) Female / Male	19 (41.3%) / 27 (58.7%)
Age, median (min, max) –years	67.0 (28, 91)
ECOG-PS –n(%) 0 / 1	34 (73.9%) / 12 (26.1%)
Disease stage –n(%)	
IIIC / IIIB /	20 (43.5%) / 9 (19.6%) /
IV/M1a / IV/M1b / IV/M1c	5 (10.9%) / 5 (10.9%) / 7 (15.2%)
Prior Chemotherapies –n(%)	
≥ 1 Prior Cancer therapy	20 (43.5%)
Chemotherapy	6 (13.0%)
Immunotherapy	15 (32.6%)
anti-PD1 ab	2 (4.3%)
Other prior therapy	2 (4.3%)
Histopathology	
Malignant melanoma	31 (67.4%)
Acral	4 (8.7%)
Mucosal	0
Nodular	4 (8.7%)
Superficial spreading	2 (4.3%)
Others	3 (6.5%)

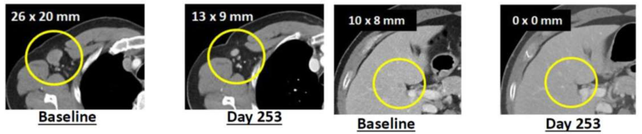
Phase II Overall Results

Summary of ≥ Grade 3 Treatment-Emergent AEs

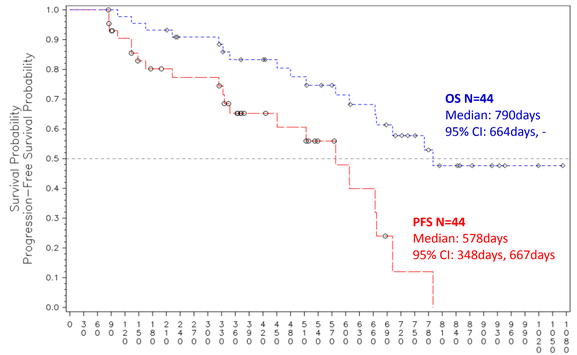
MedDRA System Organ Class N=46 n (%)	Any Relationship	C-REV-Related	Ipilimumab-Related
Number of Patients with Any TEAEs	17 (37.0%)	3 (6.5%)	10 (21.7%)
Gastrointestinal disorders	7 (15.2%)	1 (2.2%)	5 (10.9%)
Nervous system disorders	3 (6.5%)	0	0
Musculoskeletal and connective tissue disorders	3 (6.5%)	1 (2.2%)	0
Metabolism and nutrition disorders	4 (8.7%)	1 (2.2%)	1 (2.2%)
Infections and infestations	2 (4.3%)	0	0
Respiratory, thoracic and mediastinal disorders	3 (6.5%)	0	1 (2.2%)
Investigations	4 (8.7%)	0	3 (6.5%)
Vascular disorders	1 (2.2%)	1 (2.2%)	0
Blood and lymphatic system disorders	2 (4.3%)	0	0
Injury, poisoning and procedural complications	2 (4.3%)	0	0
Cardiac disorders	2 (4.3%)	0	0
Endocrine disorders	1 (2.2%)	0	1 (2.2%)
Ear and labyrinth disorders	1 (2.2%)	0	0

Response of Patient 001-040

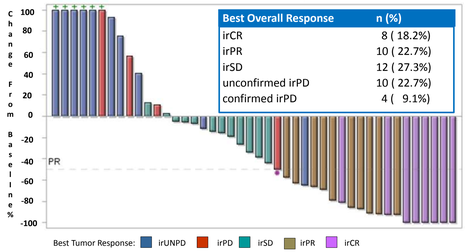
Injected Right Axilla Metastatic Lymp Node — Non-Injected Liver Segment 4A



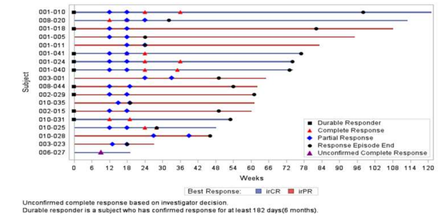
Kaplan-Meier Curve for OS and PFS



Best Percent Change in Tumor Burden at Week 24

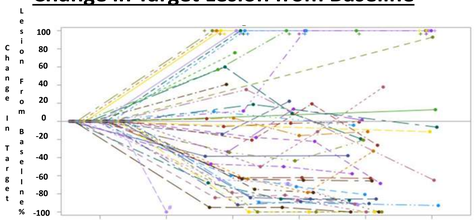


Timing of Responses Relative to C-REV Administration for Responding Patients



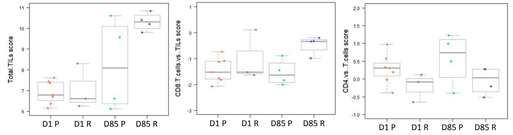
Unconfirmed complete response based on investigator decision.
Durable responder is a subject who has confirmed response for at least 182 days(6 months).

Change in Target Lesion from Baseline



[+] Percentage change from baseline in tumour lesion size exceeds +100%. Spider plot truncated for the patient at this point.
[#] Unconfirmed Complete Response based on investigator decision.
EOS – End of study includes those patients who went off-study before Week 24 or Day 169.

TILs, CD8 and CD4 After C-REV Treatment



Method:
Tumor samples were collected on Day1 and Day85 and analyzed by standard flow cytometry methods.

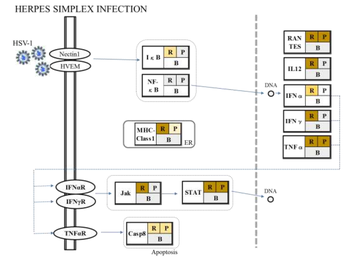
Summary:
Compared to Progressors, Responders demonstrated higher TILs score with increasing of CD8/CD4 T cell ratio, indicating that tumor antigen specific CD8 T cells played an important role in this combination therapy.

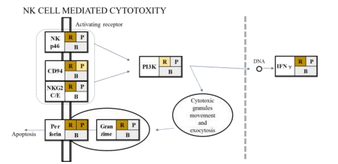
PanCancer Immune Profiling Analysis in Tumor

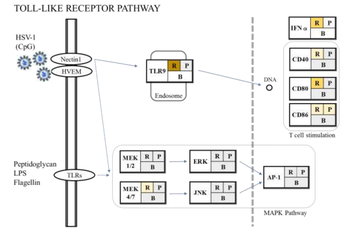
Gene expression change on Days 85

Factor	Responder	Progressor
	D85 vs. baseline	D85 vs. baseline
	Baseline R vs. P	

-2.5 0.0 2.5







Method:
Total RNA samples isolated from tumor of representative 12 of 46 patients (4 Responders and 8 Progressors) were evaluated for gene expression using the NanoString nCounter Analysis System. These data were visualized by KEGG (Kyoto Encyclopedia of Genes and Genomes) Mapper.

Summary:
- After treatment, immune-related genes were drastically induced within the tumor, while the MAPK pathway was not substantially activated.
- There was no significant difference in the baseline expression between Responders and Progressors.
- Compared to Progressors, Responders demonstrated the tendency to upregulation of following genes relating to both innate and adaptive components of the cellular immune response.
  - IFNα, IFNγ and IL-12
  - TLR9; DNA sensor which recognizes CpG motif derived from HSV-1 and induce anti-virus response
  - MHC class1; Downregulated in some tumor and essential for effector T cell attack
  - CD40, CD80 and CD86; Costimulatory molecules for T cell activation.

Discussion/Conclusions

Treatment with C-REV plus ipilimumab was well-tolerated. Of 46 pts enrolled and treated: 59% men, median age 67 yrs (range 28 to 91); disease stage 20% IIIB, 43% IIIC and 37% IV; 57% were treatment naïve and 43% with ≥ 1 prior cancer therapy for unresectable/metastatic melanoma. The C-REV AE profile was similar in combination with ipilimumab as in C-REV monotherapy. 28.3% pts had treatment-related ≥G3 AEs, and the majority of ≥G3 AEs was due to ipilimumab. Of the 44 efficacy evaluable pts, irRC BORR at 24 weeks was 41% (18% irCR and 23% irPR); disease stability rate was 68% (27% irSD). Median PFS was 19 months and median overall survival was 26 months. Responding tumors exhibited an activation of the adaptive immune response with increased total tumor infiltrating lymphocytes and CD8+ T cells.

Conclusions:
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.

Acknowledgements

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