Preliminary results from a Phase II Study of Combination Treatment with HF10, a Replication-competent HSV-1 Oncolytic Virus, and Ipilimumab in Patients with Stage IIIB, IIIC, or IV Unresectable or Metastatic Malignant Melanoma

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Introduction

TaKaRa Bio Inc. is developing HF10, an oncolytic viral immunotherapy, for intratumoral injection in patients with unresectable or metastatic malignant melanoma. HF10 is a spontaneously occurring mutant of the HF strain of Herpes Simplex Virus type 1 (HSV-1) without external gene insertion. HF10 has attenuation of neurovirulence, attributable to the lack of the UL56 gene. In preclinical models, in addition to local oncolytic tumor destruction, systemic antitumor immune response was observed.

Phase 2 Study Design

Study Objectives

- Evaluate the efficacy, safety and tolerability of HF10 at 1x10^7 $TCID_{50}$ /mL in combination with 3mg/kg ipilimumab in patients with Stage IIIB, Stage IIIC, or Stage IV unresectable or metastatic malignant melanoma

Evaluations

- Evaluate best overall response rate (BORR) at Week 24
- Objective response rate (ORR) at Weeks 12, 18 ,24, 36 and 48
- Progression-free survival (PFS)
- 1-year survival rate
- Tumor response using mWHO and irRC

Key Inclusion Criteria

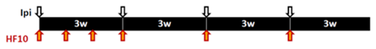
- Stage IIIB, IIIC or IV unresectable/unresected or histologically confirmed diagnosis of metastatic malignant melanoma
- Measurable (mWHO & irRC) superficial tumor suitable for injection
- Ipilimumab-eligible patients including patients previously treated with antitumor agents other than i.v. Ipilimumab.
- Adequate hepatic, renal, bone marrow function
- ECOG 0, 1, 2
- Life expectancy ≥24 weeks
- No known bleeding diathesis or coagulopathy

Study Treatment

- Intratumoral injection of HF10 at 1x10^7 $TCID_{50}$ /mL in combination with intravenous infusions of 3mg/kg ipilimumab .
- Up to 5.0mL of HF10, the injection volume to be adjusted based on the size of tumor mass

1 x10^7 $TCID_{50}$/mL dose of HF10 + 3 mg/kg ipilimumab

1-week intervals for the first 4 injections; 3-week intervals for the remaining 2 injections.



Patients may continue to receive HF10 at 1 x 10^7 $TCID_{50}$/mL alone for up to an additional 13 injections (total of 19 injections = 1 year)

Phase 2 Overall Results

Table 1: Patient Demographics

Characteristics	N (%)	Characteristics	N (%)
Age (Years)		Sex	
Median	67	Male	27 (59%)
Range	29-92	Female	19 (41%)
ECOG Status	N (%)	Disease Stage	N (%)
0	34 (74%)	IIIB	9 (20%)
1	12 (26%)	IIIC	20 (43%)
2	0 (0%)	IV	17 (37%)
HSV-1 antibody	N (%)	Prior Cancer Therapy ≥ 1	N (%)
(+)	30 (65%)	Yes	21 (46%)
(-)	16 (35%)	No	25 (54%)

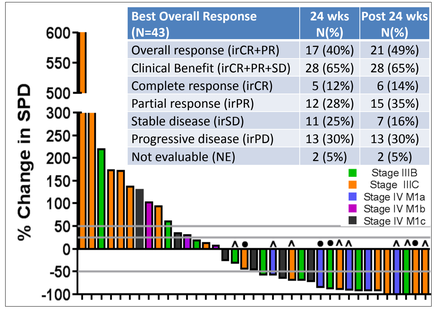
Table 2: Safety Summary

Treatment-Emergent Adverse Events (TEAEs)	Number of Patients (%)
Safety evaluable patients	46
With any TEAEs	46 (100%)
With any TEAEs related to HF10	42 (91%)
With severity ≥ Gr 3 for HF10 related TEAEs	4 (9%)
With any TEAEs related to Ipilimumab	43 (93%)
With severity ≥ Gr 3 for Ipilimumab related TEAEs	10 (22%)
With any serious, HF10 related TEAEs	2 (4%)
With any serious, Ipilimumab related TEAEs	9 (20%)
With any serious, unrelated TEAEs	6 (13%)
Who discontinued drug due to HF10 related TEAEs	0 (0%)

Table 3: Safety Profile

HF10 Related TEAEs	Number of Patients (%)
Safety evaluable patients	46
Number of patients with TEAEs	42 (91%)
Chills	6 (14%)
Fatigue	14 (33%)
Headaches	4 (10%)
Injection Site reaction	3 (7%)
Malaise, Nausea, Pruritus	12 (29%)
Events experienced by a single patient, each: - Dysqeusia - Erythema - Abscess	3 (7%)

Figure 1: Phase 2 Maximal Change in Tumor Burden

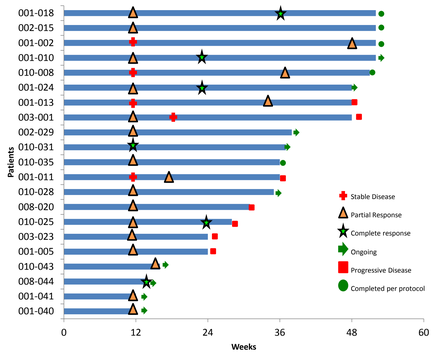


* patient has not reached 24 wks of treatment ^patient has not reached 48 weeks of treatment

Table 4: Stage IV (TNM) Responses

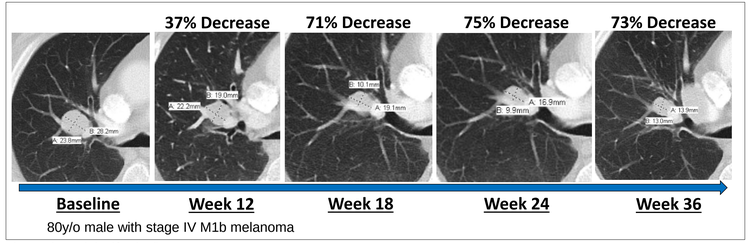
TNM Staging (n=15)	CR N (%)	PR N (%)	SD N (%)	PD N (%)
M1a	1 (7%)	4 (27%)	0	0
M1b	0	1 (7%)	1 (7%)	2 (13%)
M1c	0	2 (13%)	2 (13%)	2 (13%)

Figure 2: Timing and Duration of Response



Phase 2 Individual Results

Figure 3: Patient 001-005 Responses in Non-Injected Lesion (Lung)



*percent change calculated from baseline

Figure 4: Response of Patient 010-008

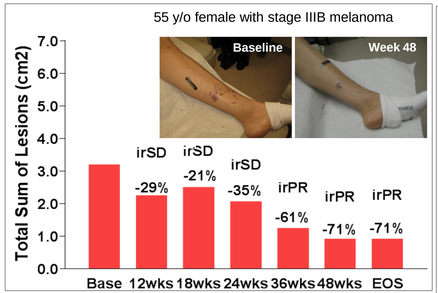


Figure 5: Response of Patient 001-024

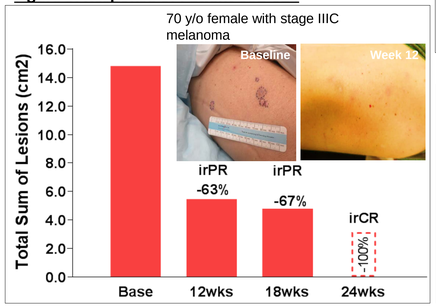


Figure 6: Early Response Patient 006-027

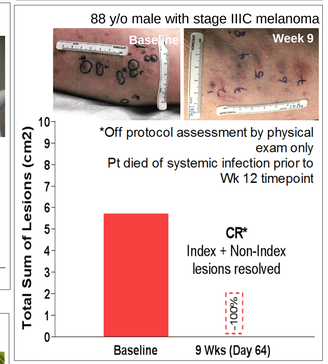
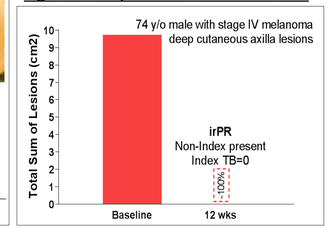


Figure 7: Response of Patient 008-020



Discussion/Conclusions

Phase 2 Trial

Treatment with HF10 plus ipilimumab was well-tolerated. Grade 3 or greater HF10-related adverse events were infrequent (9%). HF10-related adverse events did not lead to treatment discontinuation. There were no significant differences in adverse events between HSV-1+ and HSV-1- patients at baseline. Majority of HF10-related AEs were ≤grade 2, similar to HF10 monotherapy and consistent with other oncolytic viruses. No DLTs reported. There were four grade 4 AEs reported, none were treatment-related. 30.4% of patients had grade 3 AEs. HF10-related Grade 3 AEs (n=4 patients) were: left groin pain, a thromboembolic event and lymphedema; hypoglycemia; and diarrhea. 46% of patients had ≥1 prior cancer therapy. Of the 17 patients with stage IV, 25% had M1a, 31% M1b, 44% M1c. Of 43 efficacy evaluable patients, preliminary BORR at 24 weeks by irRC is 40% (12% CR, 28% PR), clinical benefit rate is 65% (25% SD). 8 responders (53%) were Stage IV. 5 responders (33%) were ≥2nd line. Overall study BORR, including those after 24 weeks, by irRC is 49% (14% CR, 35% PR), clinical benefit rate is 65% (16% SD). (Data cut-off 10May2016)

Conclusions

The results indicate ipilimumab plus HF10 does not exacerbate ipilimumab toxicity and the combination is safe and well tolerated. Preliminary efficacy evaluation suggests HF10 plus ipilimumab has both local and systemic antitumor activity and substantially improves the response rate of ipilimumab alone. HF10 plus ipilimumab is a potential novel therapeutic approach for metastatic melanoma.

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