Tumor response from Phase II study of combination treatment of intratumoral HF10, a replication - competent HSV-1 oncolytic virus, and ipilimumab in patients with stage IIIB, IIIC, or IV unresectable or metastatic melanoma

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Abstract #1872

Introduction & Design

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 is replication-competent, and exhibits reduced neuroinvasiveness. In preclinical models, in addition to local oncolytic tumor destruction, systemic antitumor immune response was observed.

Study Objectives

- Evaluate the efficacy, safety and tolerability of HF10 at 1x10^7 $TCID_{50}$ /mL in combination with 3mg/kg ipilimumab (ipi) 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)
- Durable response rate
- 1-year survival rate
- Tumor response using mWHO and irRC

Key Inclusion Criteria

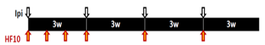
- Stage IIIB, IIIC or IV unresectable histologically confirmed diagnosis of metastatic malignant melanoma
- Measurable (mWHO & irRC) non-visceral lesions
- Ipi-eligible patients including patients previously treated with antitumor agents other than i.v. Ipi.
- Adequate hepatic, renal, and bone marrow function
- 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, 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)

Patient Population & Overall Response

Table 1: Patient Demographics

Total number of patients enrolled (N) = 46 patients

Characteristics	N (%)	Characteristics	N (%)
Age (Years)		Sex	
Median	67	Male	27 (59%)
Range	29-92	Female	19 (41%)
ECOG Status		Disease Stage	
0	34 (74%)	IIIB	9 (20%)
1	12 (26%)	IIIC	20 (43%)
2	0 (0%)	IV	17 (37%)
HSV-1 antibody		≥ 1 Prior Cancer Therapy	
(+)	30 (65%)	Yes	20 (43%)
(-)	16 (35%)	No	26 (57%)

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	2 (5%)
Nausea	6 (14%)
Pruritus	6 (14%)
Events experienced by a single patient, each: - Dysqeusia - Erythema - Abscess	3 (7%)

Table 4: Best Overall Response Rate

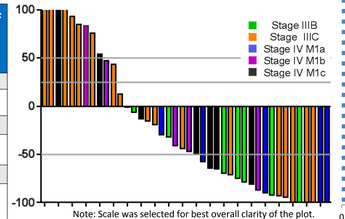
Best Overall Response (N=46)	24 weeks (N%)	Post 24 Weeks (N%)
Overall Response (irCR + irPR)	19 (41%)	22 (48%)
Clinical Benefit (irCR +irPR+irSD)	30 (65%)	30 (65%)
Complete Response (irCR)	7 (15%)	9 (20%)
Partial Response (irPR)	12 (26%)	13 (28%)
Stable Disease (irSD)	11 (24%)	8 (17%)
Progressive Disease (irPD)	13 (28%)	13 (28%)
Not Evaluable (NE)	3(7%)	3 (7%)

Table 5: Prior Therapy Responses

Prior Therapy (n=46)	CR N(%)	PR N (%)	CR+PR N (%)	SD N (%)	PD N (%)	NC N(%)
Treatment Naïve	5 (19%)	9 (35%)	14 (54%)	3 (12%)	7 (27%)	2 (8%)
≥1 prior therapy	4 (20%)	4 (20%)	8 (40%)	5 (25%)	6 (30%)	1 (5%)

Response Analysis

Figure 1: Maximum Change in Tumor Burden in Index lesions



Note: Scale was selected for best overall clarity of the plot. Progression beyond 100% is not displayed.

Figure 2: Timing and Duration of Response

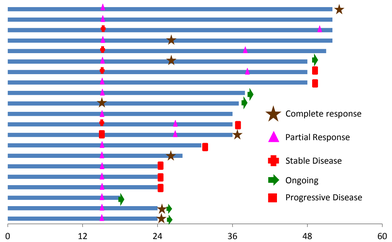
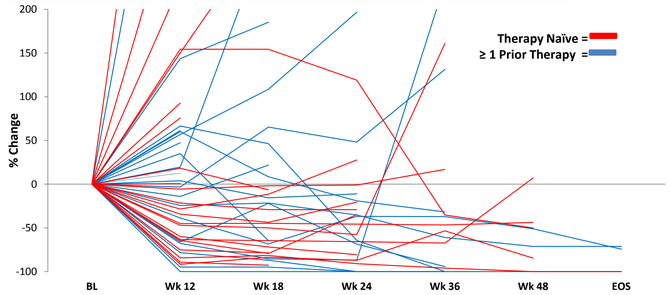
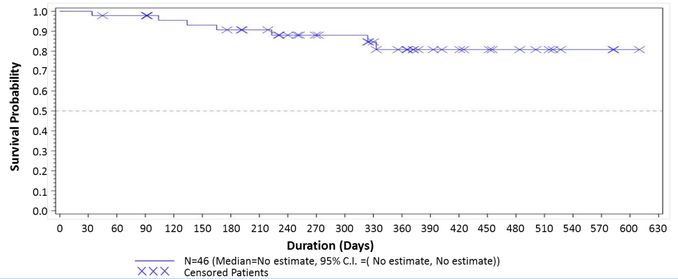


Figure 3: Response in Therapy Naïve vs. Patients with ≥ 1 Prior Therapy



Note: Scale was selected for best overall clarity of the plot. Progression beyond 200% is not displayed.

Figure 4: Kaplan–Meier Curve for Overall Survival in the Safety Evaluable Population



Discussion/Conclusions

Treatment with HF10 plus ipilimumab was well tolerated. Of 46 pts treated: 59% men; median age 67 yrs (range 29-92 yrs); disease stage 20% IIIB, 43% IIIC and 37% IV. Of all patients, 43% with ≥1 prior cancer therapy. Of the 17 patients with stage IV, 25% had M1a, 31% M1b, 44% M1c. Majority of HF10-related AEs were ≤G2, similar to HF10 monotherapy and consistent with other oncolytic viruses. No DLTs reported. 4 G4 AEs reported, none were treatment-related. 30.4% of pts had G3 AEs. HF10-related G3 AEs (n=4) were: left groin pain, a thromboembolic event and lymphedema; hypoglycemia; and diarrhea. In 26 treatment-naïve pts BORR was 54% (19% CR, 35% PR) and in 20 pts who had failed at least 1 or more therapies, BORR was 40% (20% CR, 20% PR). Of 44 efficacy evaluable pts, preliminary BORR at 24 wks by irRC was 41% (15% CR, 26% PR), disease stability rate was 65% (24% SD). 8 responders (53%) were Stage IV. 5 responders (33%) were ≥2nd line. Overall study BORR, including those after 24 weeks, by irRC was 48% (20% CR, 28% PR), disease stability rate was 65% (17% SD). This evaluation suggests HF10+ipi substantially improves (48%) the response rate of ipi alone (11%) (Hodi et. al., NEJM 2010;363:711-723).

Conclusions

HF10 + ipi does not exacerbate ipi toxicity and the combination is safe and well tolerated. Compared to historical ipi treatment, HF10 appears to have an improved response rate, with promising response rates in both treatment-naïve and previously treated pts. HF10+ipi is a potential novel therapeutic approach for metastatic melanoma.

Acknowledgements

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