Topline Results from Phase II of Combination Treatment with Canerpaturev (HF10), an Oncolytic Viral Immunotherapy, and Ipilimumab in Patients with Unresectable or Metastatic Melanoma after Anti-PD-1 Therapy

 # 1267P

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Introduction

Canerpaturev (C-REV, formerly HF10) is an oncolytic, spontaneous mutant of HSV-1, and is one of immunotherapies that combine direct tumor cell killing with immune modulation. Preclinical studies in tumor-bearing mouse model demonstrated that anti-CTLA-4 antibody with C-REV showed a higher rate of complete tumor disappearance and significant improvement in the median overall survival compared to either monotherapy. The Phase II trial of combination treatment with C-REV and ipilimumab (Ipi: anti-CTLA-4 antibody) was designed to assess the efficacy and safety of patients with pretreated unresectable or metastatic malignant melanoma .

Methods

Study Design

SCREENING

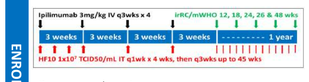
Key Eligibility Criteria
Patients with
- pretreated unresectable or metastatic melanoma (Stage IIIB, IIIC, or IV:AJCC 7th edition)
- Injectable/ measurable lesion
- Adequate organ function
- ECOG PS 0-2
- Expected life ≥ 24w
- No known bleeding diathesis or coagulopathy

ENROLLMENT

ENROLLMENT

Ipilimumab 3mg/kg IV

C-REV up to 5 mL
1x10^7 TCID$_{50}$/mL IT



Primary endpoint:
- Best overall response rate by irRC at week 24

Key secondary endpoints:
- Safety and tolerability
- Objective response rate by irRC, mWHO criteria and RECIST (Ver.1.1)
- Progression-free survival

END OF TREATMENT

FOLLOW-UP

Results

Analysis set, n	Enrollment, 28	Safety analysis set, 28	Efficacy analysis set, 27*

*Did not have a post baseline tumor assessment; n=1

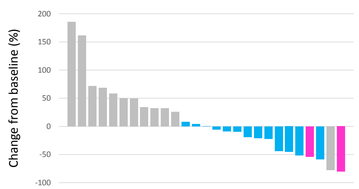
Patient Characteristics (N=28)	n (%)
Sex – n (%) Female / Male	16 (57%) / 12 (43%)
Age, median (min, max) -years	67 (31, 81)
Elderly – n (%) < 65 / 65 ≤	11 (39.3%) / 17 (60.7%)
ECOG-PS –n(%) 0 / 1 / 2	23 (82.1%) / 4 (14.3%) /1 (3.6%)
Disease stage (AJCC 7th edition) –n(%)	
IIIB / IIIC / IV	2 (7.1%) / 8 (28.6%) / 18 (64.3%)
M0 /M1a / M1b / M1c	10 (35.7%) /6 (21.4%) / 2 (7.1%) /10 (35.7%)
Prior anti-cancer therapies –n(%)	
Anti-PD1 ab / Except for Anti-PD1 ab	25 (89.3%) / 3 (10.7%)
Clinical Type –n (%)	
ALM / NM / SSM / Mucosal	11 (39.3%) / 5 (17.9%) / 3 (10.7%) / 6 (21.4%)

Phase II Overall Results

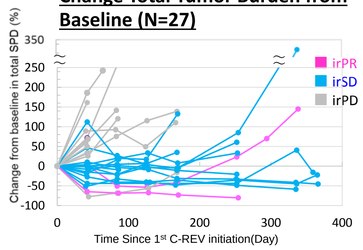
Safety Summary (N=28)

Treatment-Emergent Adverse Events (TEAEs)	n (%)
Any grade TEAEs	28 (100.0%)
Grade 3 or 4 TEAEs	14 (50.0%)
Any Severe TEAEs	16 (57.1%)
Grade 3 or 4 C-REV + Ipi-Related TEAEs	10 (35.7%)
Grade 3 or 4 C-REV-Related TEAEs	6 (21.4%)
Grade 3 or 4 Ipi-Related TEAEs	10 (35.7%)
TEAEs-Related death	0 (0.0%)

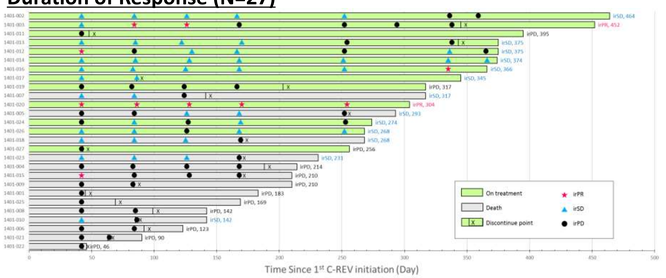
Best Percent Changes of Tumor Burden in Total Tumor (N=27)



Change Total Tumor Burden from Baseline (N=27)



Duration of Response (N=27)



Incidence of Study Treatment-Related ≥ Grade 3 TEAEs (N=28)

TEAEs	n (%)
Hyponatraemia	3 (10.7%)
Adrenal insufficiency	2 (7.1%)
Colitis	1 (3.6%)
Amylase increased	1 (3.6%)
Constipation	1 (3.6%)
Hepatic function disorder	1 (3.6%)
Lipase increased	1 (3.6%)
Malaise	1 (3.6%)
Muscle weakness lower limb	1 (3.6%)
Nausea	1 (3.6%)
Toxicoderma	1 (3.6%)
White blood cell decreased	1 (3.6%)

Efficacy Summary (N=27)

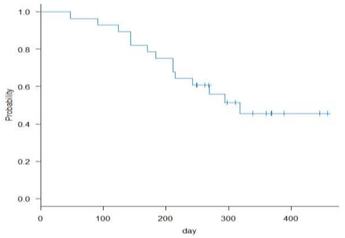
Overall Response - irRC	n (%)
Objective Response Rate (ORR*) / 90% CI	2 (7.4%) /1.3-21.5
Disease Control Rate (DCR**) / 90% CI	15 (55.6%) / 38.2-72.0
Best Overall Response Rate (BORR)	
Complete Response (irCR)	0 (0.0%)
Partial Response (irPR)	2 (7.4%)
Stable Disease (irSD)	13 (48.2%)
Unconfirmed Progressive Disease (unconfirmed irPD)	6 (22.2%)
Confirmed Progressive Disease (confirmed irPD)	6 (22.2%)

*ORR: irCR + irPR, **DCR: irCR + irPR + irSD

Subgroup Analysis: M-Stage, Clinical Type (N=27)

	n	irPR n (%)	irSD n (%)	irPD n (%)
M-Stage				
M0	10	2 (20.0%)	5 (50.0%)	3 (30.0%)
M1a	5	0 (0.0%)	3 (60.0%)	2 (40.0%)
M1b	2	0 (0.0%)	1 (50.0%)	1 (50.0%)
M1c	10	0 (0.0%)	4 (40.0%)	6 (60.0%)
Clinical Type				
ALM	10	1 (10.0%)	6 (60.0%)	3 (30.0%)
NM	5	0 (0.0%)	3 (60.0%)	2 (40.0%)
SSM	3	0 (0.0%)	0 (0.0%)	3 (100%)
Mucosal	6	1 (16.7%)	2 (33.3%)	3 (50.0%)
Others	3	0 (0.0%)	2 (66.7%)	1 (33.3%)

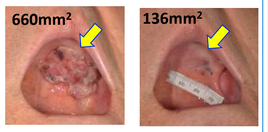
Kaplan-Meier analysis of overall survival (N=28)



		95% CI
1 y survival rate	45.7%	(25.2 – 64.0)
MST	318Days	(211 - NA)

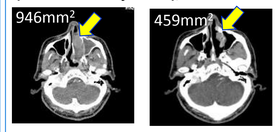
irRC Response (irPR) of Patient 1401-020

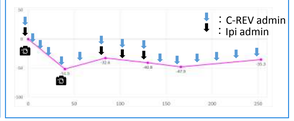
77 / Male, Stage IIIC, Mucosal Melanoma
Prior therapy : Nivolumab



irRC Response (irSD) of Patient 1401-012

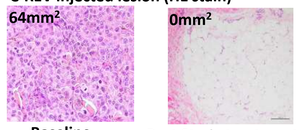
74 / Male, Stage IIIC, Mucosal Melanoma
Prior therapy : Interferon beta (intradermal injection), Nivolumab

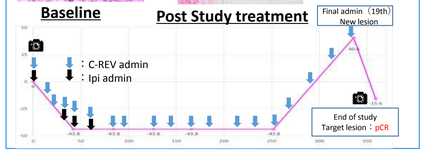




Pathological Response (pCR) of Patient 1401-002

31 / Male, Stage IIIC, Nodular Melanoma
Prior therapy : PEG-IFNα, Interferon beta (intradermal injection), Nivolumab
C-REV injected lesion (HE stain)





Summary of Results/Conclusions

Summary: Of 28 pts enrolled and treated as of the data cut-off 31 Aug 2018: The median age was 67 yrs (range: 31 to 81) and 43% pts were male. Disease stage was 7.1% IIIB, 28.6% IIIC and 64.3% IV. The most common subtype was 39.3% acral lentiginous and 21.4% mucosal melanoma. All pts were received prior therapies: 89.3% PD-1 monotherapy, 11% DTIC and 7% DAVFeron (DTIC, ACNU, Vincristine, and intradermal Interferon beta). 21.4% had ≥G3 C-REV-related AEs; adrenal insufficiency, constipation, hepatic function disorder, malaise, muscle weakness in lower limb, Nausea, and toxic skin eruption. Although BORR by irRC was 7.4% (2/27), and disease control rate reached relatively high 55.6% (15/27). One of patients with SD achieved pCR at the end of study. Median OS was 318 days.

Conclusions: The combination of C-REV with ipi did not show the exacerbate ipi toxicity, and had a favorable benefit/risk profile in Japanese pts who had received prior therapies mainly of PD-1. It is recently well-known that the response to ipi after anti-PD-1 therapy was unsatisfactory and associated with a high frequency of severe irAEs, in particular Asian populations.[1), 2)] The presented response data are encouraging compared to that of the Ipi monotherapy. C-REV+ipi therapy has potential to become a new 2nd line treatment for melanoma.

Ref) Efficacy of Ipi monotherapy after Nivolumab in Japanese patients with melanoma

	Fujisawa Y. et al. [1)]	Sato M. et al. [2)]
Number of Patients	60	9
≥ Grade 3 AEs	33 (55.0%)	2 (22%)
ORR	2 (3.6%)	0 (0.0%)
DCR	9 (16.3%)	1 (11.1%)
MST	223 Days	-

Acknowledgements

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Reference

1) Fujisawa Y, et al. J Dermatol Sci. 2018 Jan;89(1):60-66.
2) Sato M,et al. J Dermatol. 2018 Apr 14.

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